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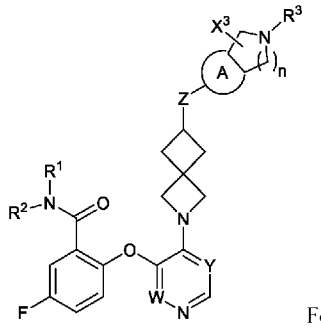
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(54) Title: ARYL ETHER ANALOGS AS INHIBITORS OF THE MENIN-MLL INTERACTION

(57) Abstract: The present disclosure is directed to inhibitors of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, of the interaction of menin with MLL and MLL fusion proteins, pharmaceutical compositions containing the same, and their use in the treatment of cancer and other diseases mediated by the menin-MLL interaction.



Formula (I).

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ARYL ETHER ANALOGS AS INHIBITORS OF THE MENIN-MLL INTERACTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/579,241, filed on August 28, 2023; U.S. Provisional Application No. 63/620,520, filed on January 12, 2024; and U.S. Provisional Application No. 63/651,602, filed on May 24, 2024, the entire contents of each of which are incorporated herein by reference.

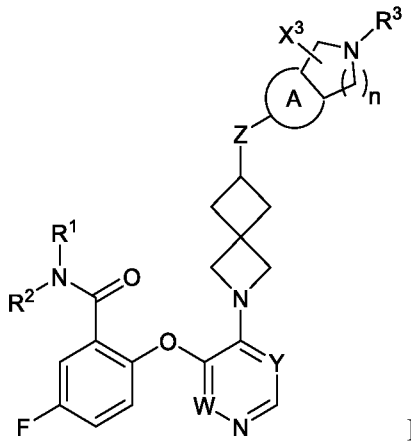
BACKGROUND

The mixed-lineage leukemia (MLL), also known as KMT2A, gene encodes a protein that is a histone methyltransferase that is mutated in clinically and biologically distinctive subsets of acute leukemia. Rearranged mixed lineage leukemia (MLL-r) involves recurrent translocations of the 11q23 chromosome locus which lead to an aggressive form of acute leukemia with limited therapeutic options. These translocations target the *MLL* gene creating an oncogenic fusion protein comprising the amino-terminus of MLL fused in frame with more than 60 different fusion protein partners. Menin, a ubiquitously expressed, nuclear protein encoded by the multiple endocrine neoplasia type 1 (*MEN1*) tumor suppressor gene, has a high affinity binding interaction with MLL fusion proteins and is an essential co-factor of oncogenic MLL-r fusion proteins. Disruption of this interaction leads to selective growth inhibition and apoptosis of MLL-r leukemia cells both *in vitro* and *in vivo*.

The interaction between menin and MLL or MLL fusion proteins is an attractive target for therapeutic intervention, and there is a need for novel agents that inhibit the menin-MLL interaction for the treatment of various diseases and conditions, including leukemia, other cancers, and diabetes.

SUMMARY

In one aspect, the present disclosure is directed to a compound of Formula (I),



Formula (I),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-

C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

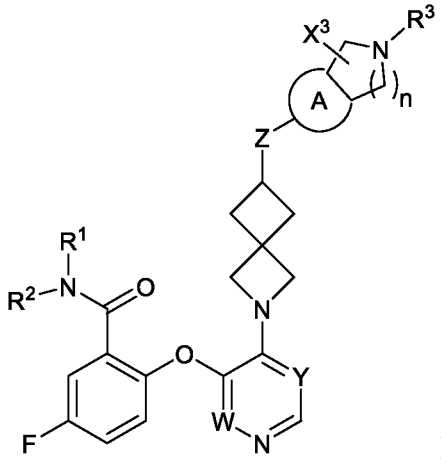
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (III),



Formula (III),

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

W is N or CH;

Y is N or CH;

R^1 is C_1-C_6 alkyl or C_3-C_{12} cycloalkyl, wherein the C_1-C_6 alkyl or the C_3-C_{12} cycloalkyl is optionally substituted with one or more halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl;

X^3 is H or C_1-C_6 alkyl;

R^3 is H or C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, or R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected;

each R^{3a} is independently $N(R^{4a})(R^{4b})$ or 3- to 12-membered heterocyclyl, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituent independently selected from C_1-C_6 alkyl and $O(R^{4a'})$;

each R^{4a} and R^{4b} is independently C_1-C_6 alkyl;

$R^{4a'}$ is H; and

n is 1 or 2.

In one aspect, the present application relates to a pharmaceutical composition comprising a compound of the application, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

In one aspect, the present application relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the application, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier.

In one aspect, the present application relates to a pharmaceutical composition comprising a compound of the application, and a pharmaceutically acceptable carrier.

In one aspect, the present application relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the application, and a pharmaceutically acceptable carrier.

The present disclosure further provides a use of a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, or a stereoisomer, or pharmaceutically acceptable salt thereof in a method of treating cancer in patient in need thereof.

The present disclosure further provides a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, or a stereoisomer, or pharmaceutically acceptable salt thereof for use in a method of treating a cancer in patient in need thereof.

The present disclosure further provides a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, or a stereoisomer, or pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for the treatment of a cancer in patient in need thereof. The present disclosure further provides a method of inhibiting the interaction between menin and MLL comprising contacting the menin and MLL with an effective amount of a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, or a stereoisomer, or pharmaceutically acceptable salt thereof.

The present disclosure further provides a method of treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, a stereoisomer, or a pharmaceutically acceptable salt thereof.

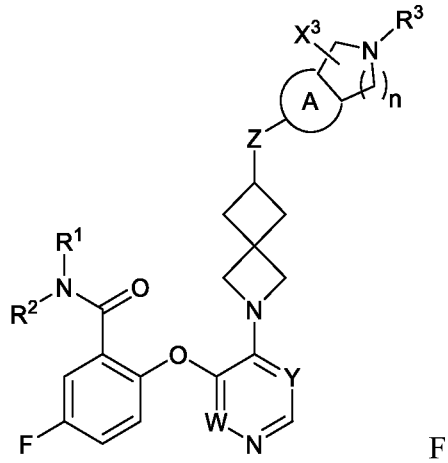
The present disclosure further provides a method of inhibiting the interaction between menin and MLL comprising contacting the menin and MLL with a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, a stereoisomer, or a pharmaceutically acceptable salt thereof.

The present disclosure further provides a method of treating cancer in a patient comprising administering to the patient an effective amount of a compound of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, a stereoisomer, or a pharmaceutically acceptable salt thereof.

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 application, illustrative methods and materials are now described. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting. 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.

DETAILED DESCRIPTION

In one aspect, the present disclosure is directed to a compound of Formula (I),



Formula (I),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-

C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

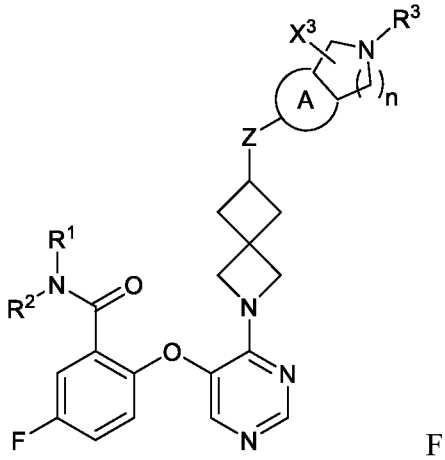
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (Ia),



Formula (Ia),

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

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$,

$N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

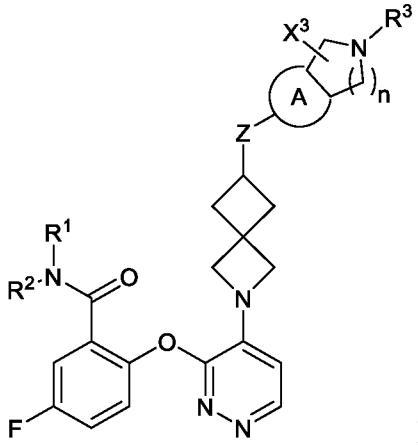
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (Ib),



Formula (Ib),

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

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

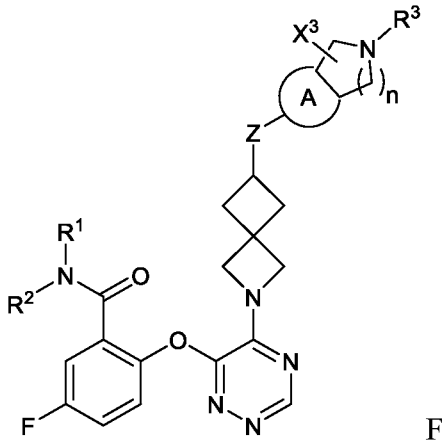
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (Ic),



Formula (Ic),

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

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-

membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, and $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

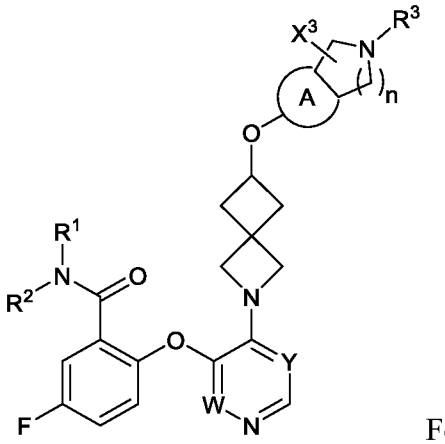
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (Id),



Formula (Id),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$,

$N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

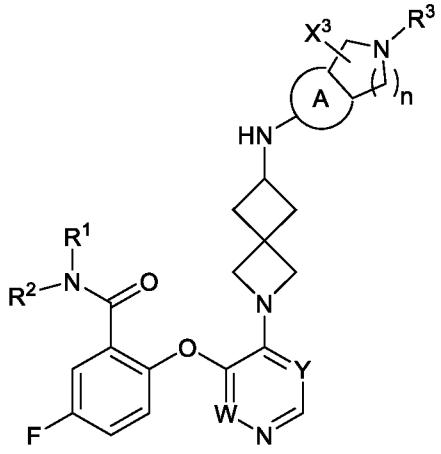
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (Ie),



Formula (Ie),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-

membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

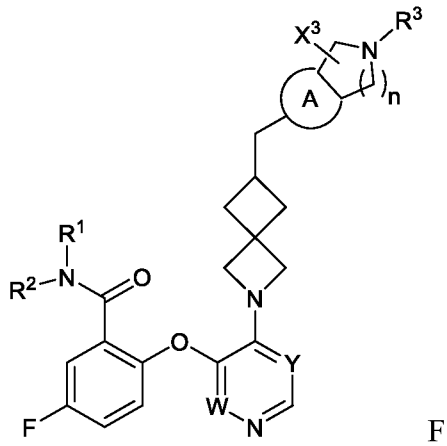
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (If),



Formula (If),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

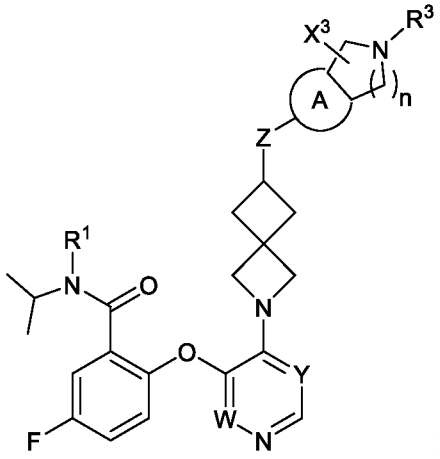
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

In one aspect, the present disclosure is directed to a compound of Formula (II),



Formula (II),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

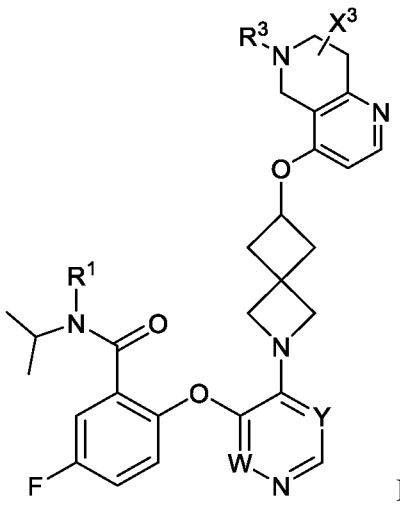
each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

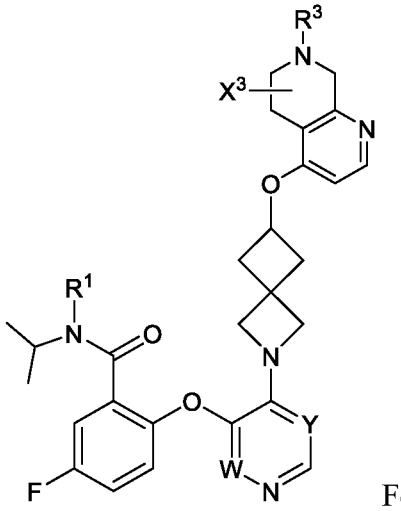
each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

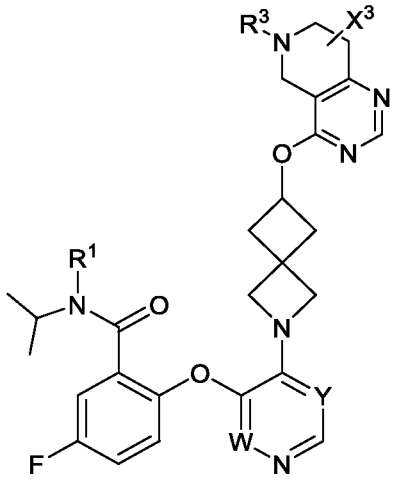
In one aspect, the present disclosure is directed to a compound of Formula (IIa), Formula (IIb), or Formula (IIc),



Formula (IIa),



Formula (IIb),



Formula (IIc),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-

membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

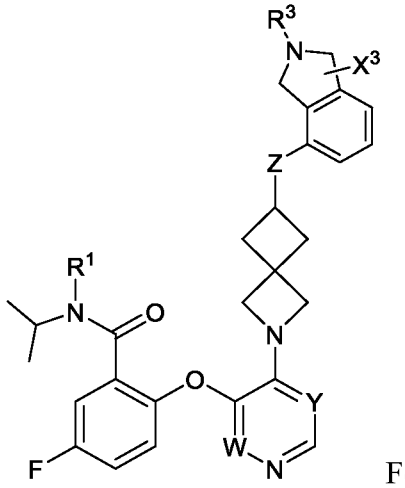
each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

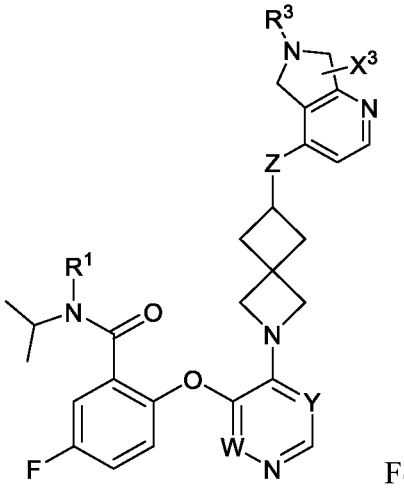
each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

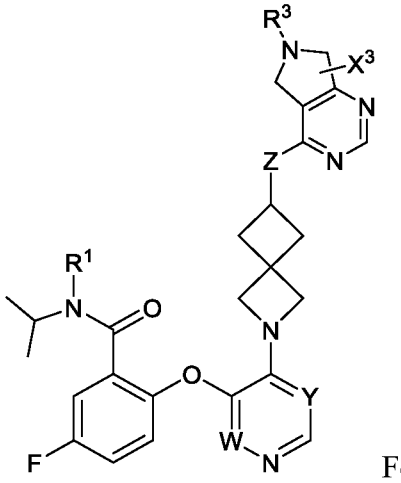
In one aspect, the present disclosure is directed to a compound of Formula (IId), Formula (IIe), or Formula (IIf),



Formula (IId),



Formula (IIe),



Formula (IIf),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

Z is O, CH_2, or NH;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-

C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

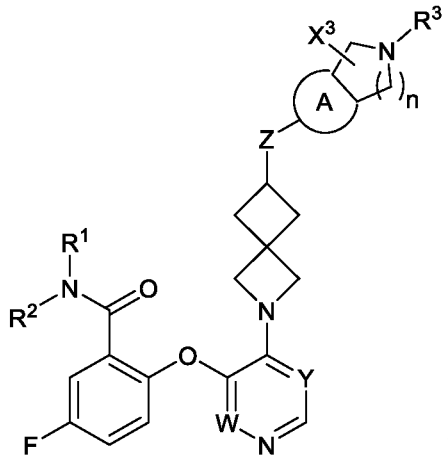
each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In one aspect, the present disclosure is directed to a compound of Formula (III),



Formula (III),

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

W is N or CH;

Y is N or CH;

R^1 is C_1-C_6 alkyl or C_3-C_{12} cycloalkyl, wherein the C_1-C_6 alkyl or the C_3-C_{12} cycloalkyl is optionally substituted with one or more halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl;

X^3 is H or C_1-C_6 alkyl;

R^3 is H or C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}; or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected;

each R^{3a} is independently $N(R^{4a})(R^{4b})$ or 3- to 12-membered heterocyclyl, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituent independently selected from C_1-C_6 alkyl and $O(R^{4a'})$;

each R^{4a} and R^{4b} is independently C_1-C_6 alkyl;

$R^{4a'}$ is H; and

n is 1 or 2.

Embodiments

For any of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III where applicable, the following embodiments are considered both alone and in conjunction with another where a stable compound is formed.

In some embodiments, W is N or CH.

In some embodiments, W is N.

In some embodiments, W is CH.

In some embodiments, Y is N or CH.

In some embodiments, Y is N.

In some embodiments, Y is CH.

In some embodiments, R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10}

aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is H.

In some embodiments, R^1 is C_1-C_6 alkyl.

In some embodiments, R^1 is C_1-C_5 alkyl.

In some embodiments, R^1 is C_1-C_4 alkyl.

In some embodiments, R^1 is C_1-C_3 alkyl.

In some embodiments, R^1 is C_1-C_2 alkyl.

In some embodiments, R^1 is methyl.

In some embodiments, R^1 is ethyl.

In some embodiments, R^1 is propyl.

In some embodiments, R^1 is isopropyl.

In some embodiments, R^1 is butyl.

In some embodiments, R^1 is *tert*-butyl.

In some embodiments, R^1 is C_1-C_6 alkyl substituted by one or more halo , OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_1-C_5 alkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_1-C_4 alkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_1-C_3 alkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_1-C_2 alkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_1-C_6 alkyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_1-C_5 alkyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_1-C_4 alkyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_1-C_3 alkyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_1-C_2 alkyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is $-CH_2-CF_3$, $-CH_2-CHF_2$, or $-CH_2-CH_2F$.

In some embodiments, R^1 is C_1-C_6 alkyl substituted by one or more CN.

In some embodiments, R^1 is C_1-C_5 alkyl substituted by one or more CN.

In some embodiments, R^1 is C_1-C_4 alkyl substituted by one or more CN.

In some embodiments, R^1 is C_1-C_3 alkyl substituted by one or more CN.

In some embodiments, R^1 is C_1-C_2 alkyl substituted by one or more CN.

In some embodiments, R^1 is $-CH_2-CN$.

In some embodiments, R^1 is C_1-C_6 alkyl substituted by one or more C_6-C_{10} aryl.

In some embodiments, R^1 is C_1-C_5 alkyl substituted by one or more C_6-C_{10} aryl.

In some embodiments, R^1 is C_1-C_4 alkyl substituted by one or more C_6-C_{10} aryl.

In some embodiments, R^1 is C_1-C_3 alkyl substituted by one or more C_6-C_{10} aryl.

In some embodiments, R^1 is C_1-C_2 alkyl substituted by one or more C_6-C_{10} aryl.

In some embodiments, R^1 is $-CH_2$-phenyl.

In some embodiments, R^1 is C_2-C_6 alkenyl.

In some embodiments, R^1 is C_2-C_5 alkenyl.

In some embodiments, R^1 is C_2-C_4 alkenyl.

In some embodiments, R^1 is C_2-C_3 alkenyl.

In some embodiments, R^1 is C_2-C_6 alkenyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_2-C_5 alkenyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_2-C_4 alkenyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_2-C_3 alkenyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_2-C_6 alkenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_2-C_5 alkenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_2-C_4 alkenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is C_2-C_3 alkenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is -CH=CF_2, or -CH=CHF.

In some embodiments, R^1 is 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 11-membered heterocyclyl.

In some embodiments, R^1 is 3- to 10-membered heterocyclyl.

In some embodiments, R^1 is 3- to 9-membered heterocyclyl.

In some embodiments, R^1 is 3- to 8-membered heterocyclyl.

In some embodiments, R^1 is 3- to 7-membered heterocyclyl.

In some embodiments, R^1 is 3- to 6-membered heterocyclyl.

In some embodiments, R^1 is 3- to 5-membered heterocyclyl.

In some embodiments, R^1 is 3- to 4-membered heterocyclyl.

In some embodiments, R^1 is 3- to 12-membered heterocyclyl substituted by one or more halo.

In some embodiments, R^1 is 3- to 11-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 10-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 9-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 8-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 7-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 6-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 5-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 4-membered heterocyclyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 3- to 12-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 11-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 10-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 9-membered heterocyclyl substituted by one or more fluorine atoms.

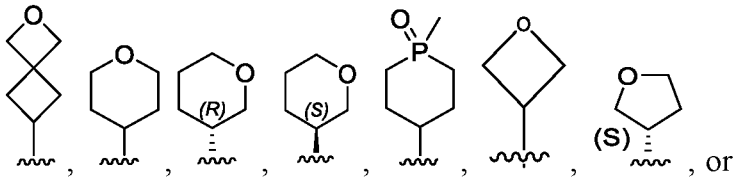
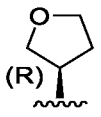
In some embodiments, R^1 is 3- to 8-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 7-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 6-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 5-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is 3- to 4-membered heterocyclyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is , or .

In some embodiments, R^1 is C_3-C_{12} cycloalkyl.

In some embodiments, R^1 is C_3-C_{11} cycloalkyl.

In some embodiments, R^1 is C_3-C_{10} cycloalkyl.

In some embodiments, R^1 is C_3-C_9 cycloalkyl.

In some embodiments, R^1 is C_3-C_8 cycloalkyl.

In some embodiments, R^1 is C_3-C_7 cycloalkyl.

In some embodiments, R^1 is C_3-C_6 cycloalkyl.

In some embodiments, R^1 is C_3-C_5 cycloalkyl.

In some embodiments, R^1 is C_3-C_4 cycloalkyl.

In some embodiments, R^1 is cyclopropyl.

In some embodiments, R^1 is cyclobutyl.

In some embodiments, R^1 is cyclopentyl.

In some embodiments, R^1 is cyclohexyl.

In some embodiments, R^1 is cycloheptyl.

In some embodiments, R^1 is cyclooctyl.

In some embodiments, R^1 is cyclopentenyl.

In some embodiments, R^1 is cyclohexenyl.

In some embodiments, R^1 is cycloheptenyl.

In some embodiments, R^1 is C_3-C_{12} cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_{11} cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_{10} cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_9 cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_8 cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or

$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_7 cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_6 cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_5 cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is C_3-C_4 cycloalkyl substituted by one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is cyclopropyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cyclobutyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cyclobutyl substituted by two methyl groups.

In some embodiments, R^1 is cyclobutyl substituted by one fluorine atom and one methyl group.

In some embodiments, R^1 is cyclobutyl substituted by two fluorine atoms and one methyl group.

In some embodiments, R^1 is cyclobutyl substituted by one OH and one methyl group.

In some embodiments, R^1 is cyclobutyl substituted by one CN and one methyl group.

In some embodiments, R^1 is cyclobutyl substituted by one methoxy group.

In some embodiments, R^1 is cyclobutyl substituted by one 5- to 10-membered heteroaryl.

In some embodiments, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group.

In some embodiments, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group.

In some embodiments, R^1 is cyclobutyl substituted by one 5- to 10-membered heteroaryl and one methyl group.

In some embodiments, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group and one methyl group.

In some embodiments, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group.

In some embodiments, R^1 is cyclopentyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cyclohexyl substituted by one or more fluorine atoms.

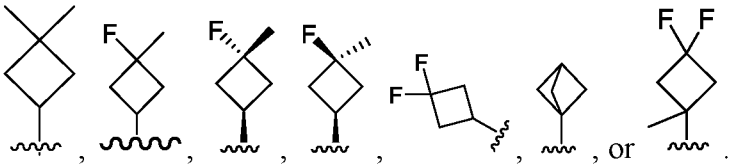
In some embodiments, R^1 is cycloheptyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cyclooctyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cyclopentenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cyclohexenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is cycloheptenyl substituted by one or more fluorine atoms.

In some embodiments, R^1 is .

In some embodiments, R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^1 is 5- to 10-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 5- to 9-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 5- to 8-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 5- to 7-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 5- to 6-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 5-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 6-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 7-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 8-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 9-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 10-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 5-membered heteroaryl optionally substituted with one or more methyl.

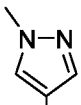
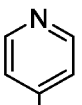
In some embodiments, R^1 is 6-membered heteroaryl optionally substituted with one or more methyl.

In some embodiments, R^1 is 7-membered heteroaryl optionally substituted with one or more methyl.

In some embodiments, R^1 is 8-membered heteroaryl optionally substituted with one or more methyl.

In some embodiments, R^1 is 9-membered heteroaryl optionally substituted with one or more methyl.

In some embodiments, R^1 is 10-membered heteroaryl optionally substituted with one or more methyl.

In some embodiments, R^1 is  or .

In some embodiments, R^2 is H.

In some embodiments, R^2 is C_1-C_6 alkyl.

In some embodiments, R^2 is C_1-C_5 alkyl.

In some embodiments, R^2 is C_1-C_4 alkyl.

In some embodiments, R^2 is C_1-C_3 alkyl.

In some embodiments, R^2 is C_1-C_2 alkyl.

In some embodiments, R^2 is methyl.

In some embodiments, R^2 is ethyl.

In some embodiments, R^2 is propyl.

In some embodiments, R^2 is isopropyl.

In some embodiments, R^2 is butyl.

In some embodiments, R^2 is *tert*-butyl.

In some embodiments, R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl.

In some embodiments, R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 12-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 11-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 10-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 9-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 8-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 7-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 6-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 5-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 4-membered heterocyclyl.

In some embodiments, R^1 and R^2 form a 3- to 12-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 11-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 10-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 9-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 8-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 7-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 6-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a 3- to 5-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

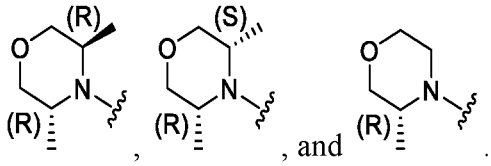
In some embodiments, R^1 and R^2 form a 3- to 4-membered heterocyclyl substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a morpholinyl group.

In some embodiments, R^1 and R^2 form a morpholinyl group substituted by one or more C_1-C_6 alkyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a morpholinyl group substituted by one or more methyl, halo, OH, or CN.

In some embodiments, R^1 and R^2 form a group selected from:



, , and .

In some embodiments, Z is O, CH_2, or NH .

In some embodiments, Z is O.

In some embodiments, Z is CH_2.

In some embodiments, Z is NH.

In some embodiments, Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to 10-membered aryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to 9-membered aryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to 8-membered aryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to 7-membered aryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is a phenyl ring.

In some embodiments, Ring A is 6- to 10-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to 9-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to 8-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is 6- to7-membered heteroaryl optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is a pyridine ring.

In some embodiments, Ring A is a pyridine ring substituted with one halo.

In some embodiments, Ring A is a pyridine ring substituted with one fluorine atom.

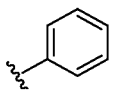
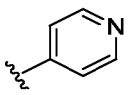
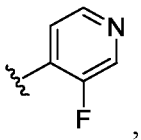
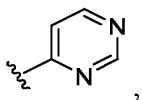
In some embodiments, Ring A is a pyrimidine ring.

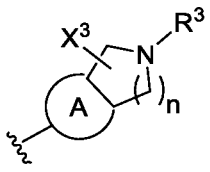
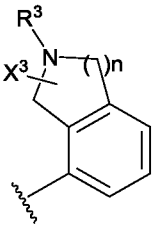
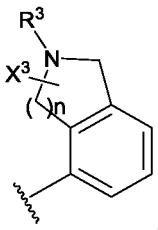
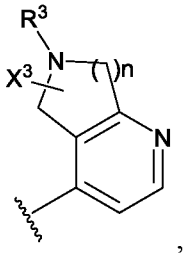
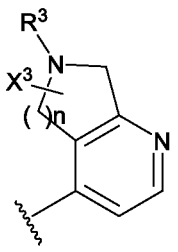
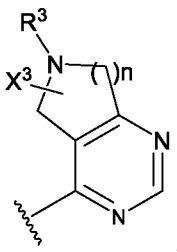
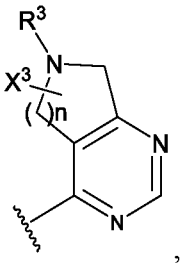
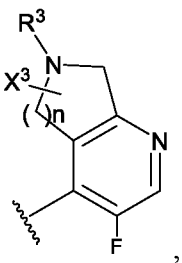
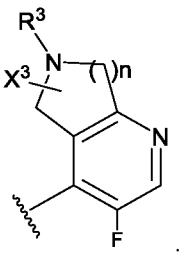
In some embodiments, Ring A is a pyridine ring optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is a pyrimidine ring optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

In some embodiments, Ring A is a pyridine ring optionally substituted with one or more fluorine atoms.

In some embodiments, Ring A is a pyrimidine ring optionally substituted with one or more fluorine atoms.

In some embodiments, Ring A is , , , or , wherein  represents a bond to Z.

In some embodiments,  is , , , , , , , or .

In some embodiments, X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$; wherein:

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is H.

In some embodiments, X^3 is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_5 alkyl.

In some embodiments, X^3 is C_1-C_4 alkyl.

In some embodiments, X^3 is C_1-C_3 alkyl.

In some embodiments, X^3 is C_1-C_2 alkyl.

In some embodiments, X^3 is methyl.

In some embodiments, X^3 is ethyl.

In some embodiments, X^3 is propyl.

In some embodiments, X^3 is isopropyl.

In some embodiments, X^3 is butyl.

In some embodiments, X^3 is *tert*-butyl.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_5 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_4 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_3 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_2 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_5 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_4 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_3 alkyl substituted by one or more -OH.

In some embodiments, X^3 is C_1-C_2 alkyl substituted by one or more -OH.

In some embodiments, X^3 is $-CH_2(OH)$, $-CH_2$-$CH_2(OH)$, or $-CH_2$-CH_2-$CH_2(OH)$.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more OR^{4a}; wherein each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-

C_{10} aryl or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_5 alkyl substituted by one or more OR^{4a}; wherein each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_4 alkyl substituted by one or more OR^{4a}; wherein each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_3 alkyl substituted by one or more OR^{4a}; wherein each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_2 alkyl substituted by one or more OR^{4a}; wherein each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is $-CH_2-OCH_3$, $-CH_2-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-OCH_3$, $-CH_2-O-CH_2-CHF_2$, $-CH_2-CH_2-CH_2-O-CHF_2$, or $-CH_2-O-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, X^3 is $-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-O-CH_2$-phenyl, or $-CH_2-CH_2-CH_2-O-CH_2$-phenyl.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more $C(=O)N(R^{4a})(R^{4b})$; wherein:

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$,

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2-N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more $C(=O)N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_5 alkyl substituted by one or more $C(=O)N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_4 alkyl substituted by one or more $C(=O)N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_3 alkyl substituted by one or more $C(=O)N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_2 alkyl substituted by one or more $C(=O)N(CH_3)_2$.

In some embodiments, X^3 is $-CH_2-C(=O)N(CH_3)_2$, $-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more $N(R^{4a})(R^{4b})$; wherein:

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$,

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_6 alkyl substituted by one or more $-N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_5 alkyl substituted by one or more $-N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_4 alkyl substituted by one or more $-N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_3 alkyl substituted by one or more $-N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_2 alkyl substituted by one or more $-N(CH_3)_2$.

In some embodiments, X^3 is $-CH_2-N(CH_3)_2$, $-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, X^3 is C_1-C_6 alkyl substituted with $S(=O)_2R^{4a}$, wherein R^{4a} is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_5 alkyl substituted with $S(=O)_2R^{4a}$, wherein R^{4a} is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_4 alkyl substituted with $S(=O)_2R^{4a}$, wherein R^{4a} is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_3 alkyl substituted with $S(=O)_2R^{4a}$, wherein R^{4a} is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_2 alkyl substituted with $S(=O)_2R^{4a}$, wherein R^{4a} is C_1-C_6 alkyl.

In some embodiments, X^3 is $-CH_2-CH_2-S(O)_2-CH_3$ or $-CH_2-CH_2-CH_2-S(O)_2-CH_3$.

In some embodiments, X^3 is C_1-C_6 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_5 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_4 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_3 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_2 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is $-CH_2-CH_2-NH-C(O)-CH_3$.

In some embodiments, X^3 is C_1-C_6 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_5 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_4 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_3 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is C_1-C_2 alkyl substituted with $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, and wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, X^3 is $-CH_2-CH_2-NH-S(O)_2-CH_3$.

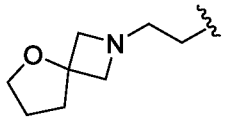
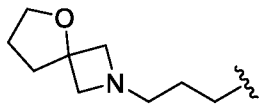
In some embodiments, X^3 is C_1-C_6 alkyl substituted with 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_5 alkyl substituted with 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_4 alkyl substituted with 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_3 alkyl substituted with 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is C_1-C_2 alkyl substituted with 3- to 12-membered heterocyclyl.

In some embodiments, X^3 is  or .

In some embodiments, R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}; wherein:

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is H.

In some embodiments, R^3 is C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl.

In some embodiments, R^3 is methyl.

In some embodiments, R^3 is -CD_3. In some embodiments, R^3 is ethyl.

In some embodiments, R^3 is propyl.

In some embodiments, R^3 is isopropyl.

In some embodiments, R^3 is butyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

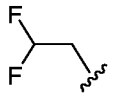
In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro.

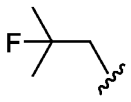
In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo. In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo. In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro. In some embodiments, R^3 is .

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo.

In some embodiments, R^3 is 2-methyl propyl, wherein the 2-methyl propyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a halo. In one embodiment, R^3 is 2-methyl propyl, wherein the 2-methyl propyl is optionally substituted by one or more R^{3a} and wherein R^{3a} is a fluoro. In some embodiments, R^3 is 

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In some embodiments, R^3 is a C_3-C_{12} cycloalkyl.

In some embodiments, R^3 is a C_3-C_{11} cycloalkyl.

In some embodiments, R^3 is a C_3-C_{10} cycloalkyl.

In some embodiments, R^3 is a C_3-C_9 cycloalkyl.

In some embodiments, R^3 is a C_3-C_8 cycloalkyl.

In some embodiments, R^3 is a C_3-C_7 cycloalkyl.

In some embodiments, R^3 is a C_3-C_6 cycloalkyl.

In some embodiments, R^3 is a C_3-C_5 cycloalkyl.

In some embodiments, R^3 is a C_3-C_4 cycloalkyl.

In some embodiments, R^3 is .

In some embodiments, R^3 is a C_3-C_{12} cycloalkyl wherein the cycloalkyl is optionally substituted by one or more R^{3a}, and wherein:

each R^{3a} is independently halo, OR^{4a}, oxo, CN, $N(R^{4a})(R^{4b})$, or C_1-C_6 alkyl, and

each R^{4a} and R^{4b} is H.

In some embodiments, R^3 is a C_3-C_{12} cycloalkyl wherein the C_3-C_{12} cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_{11} cycloalkyl wherein the C_3-C_{11} cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_{10} cycloalkyl wherein the C_3-C_{10} cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_9 cycloalkyl wherein the C_3-C_9 cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

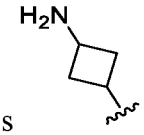
In some embodiments, R^3 is a C_3-C_8 cycloalkyl wherein the C_3-C_8 cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_7 cycloalkyl wherein the C_3-C_7 cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_6 cycloalkyl wherein the C_3-C_6 cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_5 cycloalkyl wherein the C_3-C_5 cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_4 cycloalkyl wherein the C_3-C_4 cycloalkyl is optionally substituted by one or more halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is 

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In some embodiments, R^3 is a C_3-C_{12} cycloalkyl wherein the cycloalkyl is optionally substituted by one or more R^{3a}, and wherein:

each R^{3a} is independently halo, OR^{4a}, oxo, CN, $N(R^{4a})(R^{4b})$, or C_1-C_6 alkyl, and

each R^{4a} and R^{4b} is CH_3.

In some embodiments, R^3 is a C_3-C_{12} cycloalkyl wherein the C_3-C_{12} cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_{11} cycloalkyl wherein the C_3-C_{11} cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_{10} cycloalkyl wherein the C_3-C_{10} cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_9 cycloalkyl wherein the C_3-C_9 cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

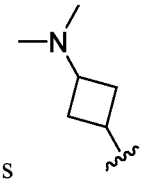
In some embodiments, R^3 is a C_3-C_8 cycloalkyl wherein the C_3-C_8 cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_7 cycloalkyl wherein the C_3-C_7 cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_6 cycloalkyl wherein the C_3-C_6 cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_5 cycloalkyl wherein the C_3-C_5 cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is a C_3-C_4 cycloalkyl wherein the C_3-C_4 cycloalkyl is optionally substituted by one or more halo, OCH_3, oxo, CN, $N(CH_3)_2$, or C_1-C_6 alkyl.

In some embodiments, R^3 is .

In some embodiments, R^3 is a 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 11-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 10-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 9-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 8-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 7-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 6-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 5-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 4-membered heterocyclyl.

In some embodiments, R^3 is a 3- to 12-membered heterocyclyl, wherein the 3- to 12-membered heterocyclyl is optionally substituted by one or more R^{3a}, wherein:

each R^{3a} is independently halo, OR^{4a}, oxo, CN, $N(R^{4a})(R^{4b})$, or C_1-C_6 alkyl, and wherein:

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl;

In some embodiments, R^3 is a 3- to 12-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OR^{4a}, oxo, CN, $N(R^{4a})(R^{4b})$, or C_1-C_6 alkyl, and wherein each R^{4a} and R^{4b} is H.

In some embodiments, R^3 is a 3- to 12-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 11-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 10-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 9-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

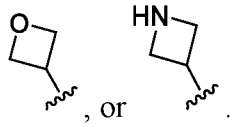
In some embodiments, R^3 is a 3- to 8-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 7-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 6-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 5-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is a 3- to 4-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein each R^{3a} is independently halo, OH, oxo, CN, NH_2, or C_1-C_6 alkyl.

In some embodiments, R^3 is 

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In some embodiments, R^3 is a 3- to 12-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 11-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 10-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 9-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

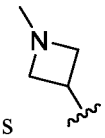
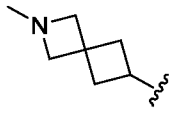
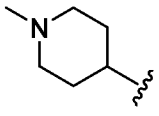
In some embodiments, R^3 is a 3- to 8-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 7-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 6-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 5-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is a 3- to 4-membered heterocyclyl that is optionally substituted by one or more R^{3a}, wherein R^{3a} is methyl.

In some embodiments, R^3 is  ,  , or  .

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein:

each R^{3a} is independently OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$,

$S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently oxo, CN, $N(R^{4a})(R^{4b})$, OR^{4a}, $C(O)O(R^{4a})$, $S(=O)_2R^{4b'}$ or C_1-C_6 alkyl; each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $C(O)O(R^{4a})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is $-CH_2$-C(O)OH, $-CH_2-CH_2$-C(O)OH, or $-CH_2-CH_2$-OMe.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more CN.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more CN.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more CN.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more CN.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more CN.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more CN.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more CN.

In some embodiments, R^3 is $-CH_2-CH_2$-CN.

In some embodiments, R^3 is methyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is $-CH_2-S(=O)_2Me$.

In some embodiments, R^3 is ethyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is $-CH_2-CH_2-S(=O)_2Me$.

In some embodiments, R^3 is ethyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is $-CH_2-CH_2-CH_2-S(=O)_2Me$.

In some embodiments, R^3 is propyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is isopropyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is *tert*-butyl substituted with one R^{3a}. In some embodiments, R^{3a} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $S(=O)_2R^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is $-CH_2-CH_2-S(=O)_2Me$.

In some embodiments, R^3 is $-CH_2-CH_2-CH_2-S(=O)_2Me$.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is H and each R^{4b} is methyl.

In some embodiments, R^3 is $-CH_2-CH_2-NH(CH_3)$, $-CH_2-CH_2-CH_2-NH(CH_3)$, $-CH_2-CH_2-CH_2-CH_2-NH(CH_3)$, or $-CH_2-CH_2-CH_2-CH_2-CH_2-NH(CH_3)$.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein each R^{4a} is methyl and each R^{4b} is methyl.

In some embodiments, R^3 is $-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is ethyl and R^{4b} is ethyl.

In some embodiments, R^3 is $-CH_2-CH_2-N(CH_2-CH_3)_2$ or $-CH_2-CH_2-CH_2-N(CH_2-CH_3)_2$.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more $N(R^{4a})(R^{4b})$, wherein R^{4a} is H and R^{4b} is H.

In some embodiments, R^3 is $-CH_2-CH_2-NH_2$, $-CH_2-CH_2-CH_2-NH_2$, $-CH_2-CH_2-C(CH_3)_2(NH_2)$.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more OH.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more OH.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more OH.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more OH.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more OH.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more OH.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more OH.

In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more OR^{4a}, wherein R^{4a} is H.

In some embodiments, R^3 is $-CH_2-CH_2-OH$, $-CH_2-CH_2-CH_2-OH$, $-CH_2-CH_2-C(CH_3)_2(OH)$, or $-CH_2-C(CH_3)_2(OH)$.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one C_1-C_6 alkyl and one OR^{4a}. In some embodiments, R^{4a} is H and C_1-C_6 alkyl is methyl. In some embodiments, R^3 is -CH_2-$C(CH_3)_2$(OH).

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one C_1-C_6 alkyl and one OR^{4a}. In some embodiments, R^{4a} is H and C_1-C_6 alkyl is methyl. In some embodiments, R^3 is -CH_2-CH_2-$C(CH_3)_2$(OH).

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one OR^{4a}. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one OR^{4a}. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one OR^{4a}. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one OR^{4a}. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one OR^{4a}. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one OR^{4a}. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is methyl substituted with one R^{3a}. In some embodiments, R^{3a} is $C(O)O(R^{4a})$, wherein R^{4a} is H, CN, or C_1-C_6 alkyl optionally substituted with C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is -CH_2-C(O)OH.

In some embodiments, R^3 is ethyl substituted with one R^{3a}. In some embodiments, R^{3a} is $C(O)O(R^{4a})$, wherein R^{4a} is H, CN, or C_1-C_6 alkyl optionally substituted with C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is -CH_2-CH_2-C(O)OH.

In some embodiments, R^3 is propyl substituted with one R^{3a}. In some embodiments, R^{3a} is $C(O)O(R^{4a})$, wherein R^{4a} is H, CN, or C_1-C_6 alkyl optionally substituted with C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is isopropyl substituted with one R^{3a}. In some embodiments, R^{3a} is $C(O)O(R^{4a})$, wherein R^{4a} is H, CN, or C_1-C_6 alkyl optionally substituted with C_6-C_{10} aryl

or $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl substituted with one R^{3a}. In some embodiments, R^{3a} is $C(O)O(R^{4a})$, wherein R^{4a} is H, CN, or C_1-C_6 alkyl optionally substituted with C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is *tert*-butyl substituted with one R^{3a}. In some embodiments, R^{3a} is $C(O)O(R^{4a})$, wherein R^{4a} is H, CN, or C_1-C_6 alkyl optionally substituted with C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

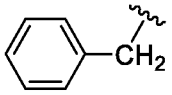
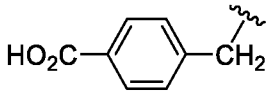
In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more

$C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is , or .

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently C_6-C_{10} aryl that is optionally substituted with one or more $C(O)OR^{4a'}$, and wherein $R^{4a'}$ is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

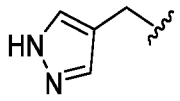
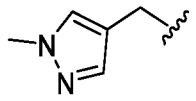
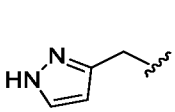
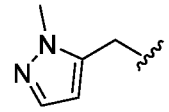
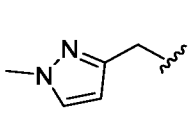
In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl. In some embodiments, R^3 is , , , , .

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 5- to 10-membered heteroaryl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently OR^{4a} or 5- to 10-membered heteroaryl. In some embodiments, each R^{4a} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently OR^{4a} or 5- to 10-membered heteroaryl. In some embodiments, each R^{4a} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently OR^{4a} or 5- to 10-membered heteroaryl. In some embodiments, each R^{4a} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently OR^{4a} or 5- to 10-membered heteroaryl. In some embodiments, each R^{4a} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently OR^{4a} or 5- to 10-membered heteroaryl. In some embodiments, each R^{4a} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

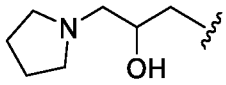
In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

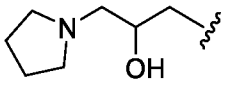
In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

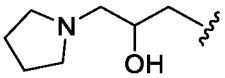
In some embodiments, R^3 is methyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

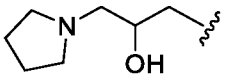
In some embodiments, R^3 is ethyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

In some embodiments, R^3 is propyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H. In some embodiments, R^3 is



(40% E1
60% E2) ,


(67% E1
33% E2) ,


(E1) , or


(E2) .

In some embodiments, R^3 is isopropyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

In some embodiments, R^3 is butyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is H.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

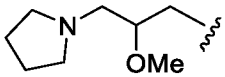
In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

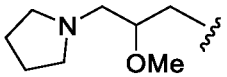
In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

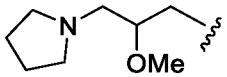
In some embodiments, R^3 is methyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is ethyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is propyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl. In some embodiments, R^3 is



(E1) ,


(+/-) , or


(E2) .

In some embodiments, R^3 is isopropyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is butyl that is substituted with one OR^{4a} and one 5- to 10-membered heteroaryl. In some embodiments, R^{4a} is methyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

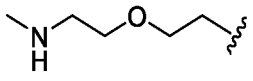
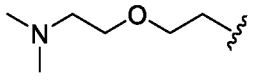
In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is  or .

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is OR^{4a}. In some embodiments, each R^{4a} is independently C_1-C_6 alkyl optionally substituted with $N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl, wherein the C_1-C_5 alkyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

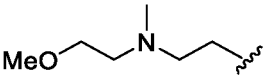
In some embodiments, R^3 is C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl, wherein the C_1-C_2 alkyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl.

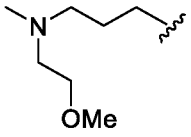
In some embodiments, R^3 is methyl, wherein the methyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl. In some embodiments, R^3 is $-CH_2-CH_2-NH_2$, $-CH_2-CH_2-NH(CH_3)$, $-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-N(CH_2-CH_3)_2$.

In some embodiments, R^3 is ethyl, wherein the ethyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl that is optionally substituted with $O(R^{4a'})$, and wherein $R^{4a'}$ is H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl. In some embodiments, $O(R^{4a'})$ is C_1-C_6 alkoxy. In some embodiments, R^3 is .

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl. In some embodiments, R^3 is $-CH_2-CH_2-CH_2-NH_2$, $-CH_2-CH_2-CH_2-NH(CH_3)$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_2-CH_3)_2$.

In some embodiments, R^3 is propyl, wherein the propyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl that is optionally substituted with $O(R^{4a'})$, and wherein each $R^{4a'}$ is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the

group consisting of H, methyl or ethyl. In some embodiments, $O(R^{4a'})$ is C_1-C_6 alkoxy. In some embodiments, R^3 is 

.

In some embodiments, R^3 is isopropyl, wherein the isopropyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl. In some embodiments, R^3 is -$CH(CH_3)(CH_2$-$NH_2)$, -$CH(CH_3)(CH_2$-$NH(CH_3))$, -$CH(CH_3)(CH_2$-$N(CH_3)_2)$, or -$CH(CH_3)(CH_2$-$N(CH_2$-$CH_3)_2)$.

In some embodiments, R^3 is butyl, wherein the butyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl. In some embodiments, R^3 is -CH_2-CH_2-CH_2-CH_2-NH_2, -CH_2-CH_2-CH_2-CH_2-$NH(CH_3)$, -CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$, -CH_2-CH_2-CH_2-CH_2-$N(CH_2$-$CH_3)_2$, or -CH_2-CH_2-$C(CH_3)_2(NH_2)$.

In some embodiments, R^3 is *tert*-butyl, wherein the *tert*-butyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl.

In some embodiments, R^3 is pentyl, wherein the pentyl is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, and wherein each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl. In some embodiments, each R^{4a} and R^{4b} is independently selected from the group consisting of H, methyl or ethyl. In some embodiments, R^3 is -CH_2-CH_2-CH_2-CH_2-CH_2-NH_2, -CH_2-CH_2-CH_2-CH_2-CH_2-$NH(CH_3)$, -CH_2-CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$, or -CH_2-CH_2-CH_2-CH_2-CH_2-$N(CH_2$-$CH_3)_2$.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$, wherein:

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

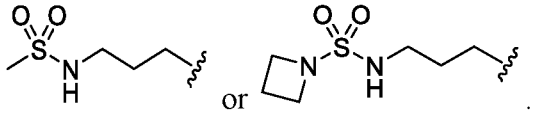
In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is



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In some embodiments, R^3 is isopropyl that is that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $S(=O)_2R^{4b'}$, wherein each $R^{4b'}$ is independently C_1-C_6 alkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

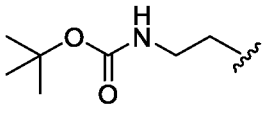
In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

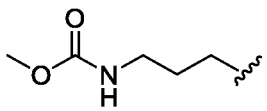
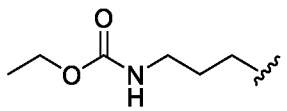
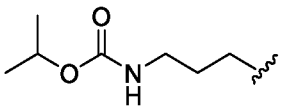
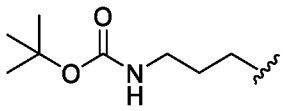
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl. In some embodiments, R^3 is .

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl. In some embodiments, R^3 is , , , or .

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)OR^{4b'}$, wherein $R^{4b'}$ is C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

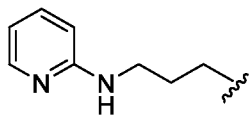
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl. In some embodiments, R^3 is 

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In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is 5- to 10-membered heteroaryl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

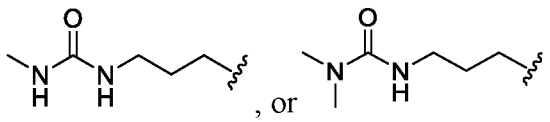
In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is


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In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)NR^{4a'}R^{4b'}$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

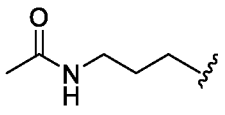
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is .

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is H and R^{4b} is $C(O)R^{4b'}$, wherein each $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

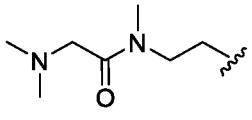
In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is .

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

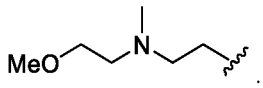
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy. In some embodiments, R^3 is



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In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with C_1-C_6 alkoxy.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

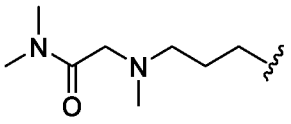
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is .

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $N(R^{4a})(R^{4b})$. In some embodiments, R^{4a} is C_1-C_6 alkyl and R^{4b} is C_1-C_6 alkyl that is optionally substituted with $C(O)N(R^{4a'})(R^{4b'})$ and wherein each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

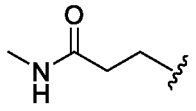
In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is .

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein R^{3a} is $C(=O)N(R^{4a})(R^{4b})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a}, wherein:

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

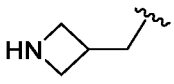
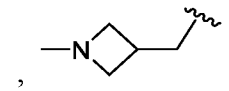
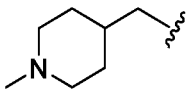
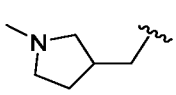
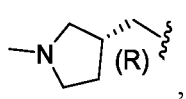
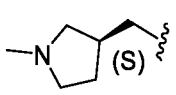
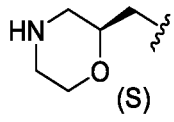
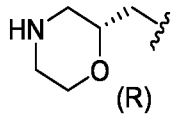
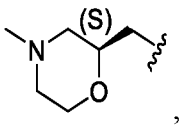
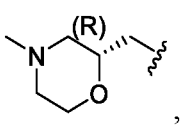
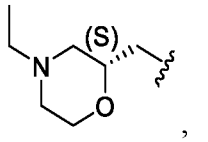
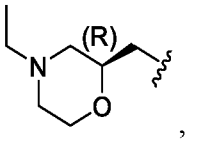
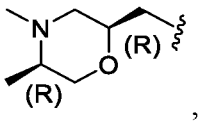
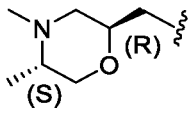
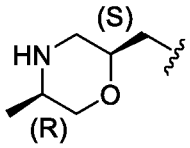
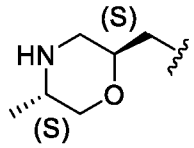
In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

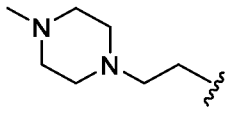
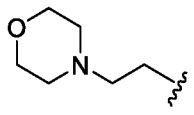
In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

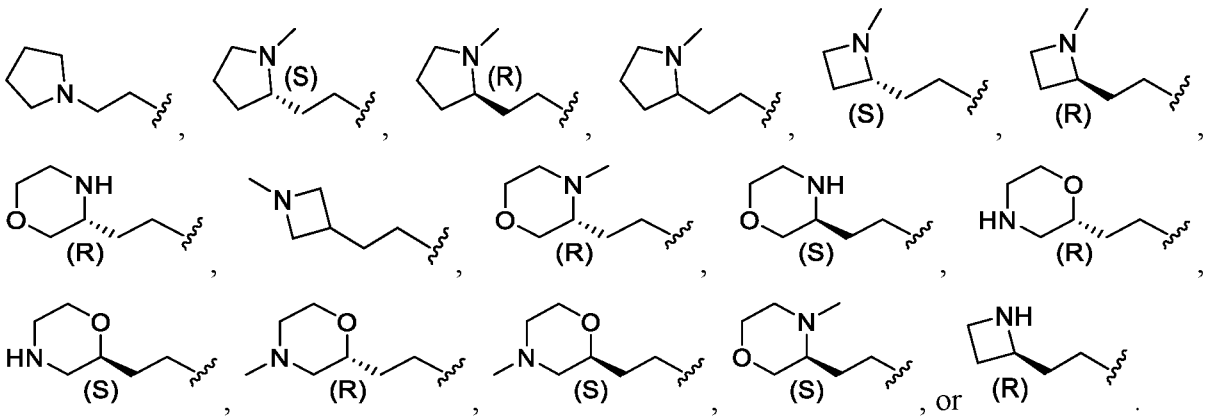
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

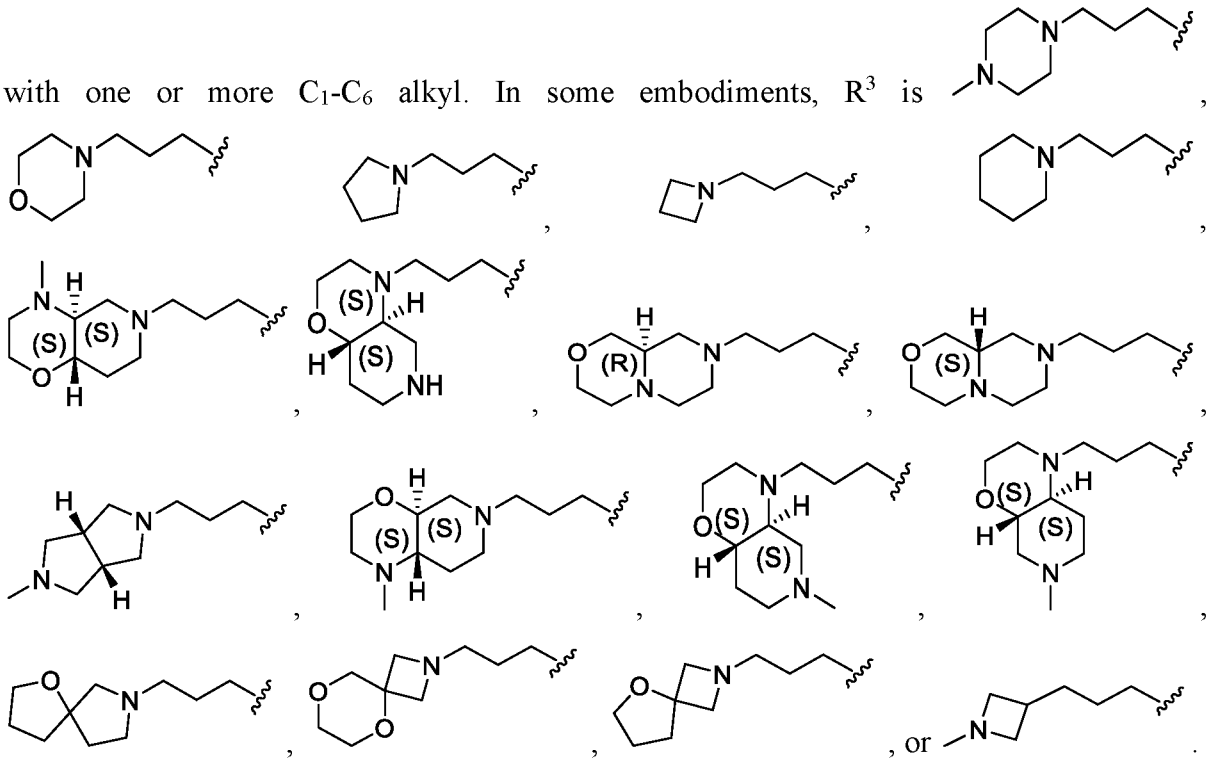
In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl. In some embodiments, R^3 is , , , , , , , , , , , , , , , and .

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl. In some embodiments, R^3 is , ,



In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl. In some embodiments, R^3 is



In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

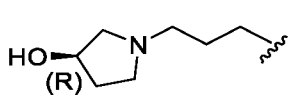
In some embodiments, R^3 is *tert*-butyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

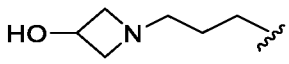
In some embodiments, R^3 is pentyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more C_1-C_6 alkyl.

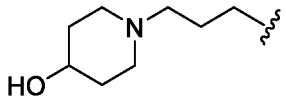
In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $O(R^{4a'})$. In some embodiments, $R^{4a'}$ is H.

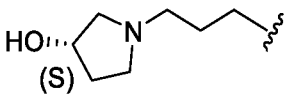
In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $O(R^{4a'})$. In some embodiments, $R^{4a'}$ is H.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $O(R^{4a'})$. In some embodiments, $R^{4a'}$ is H. In some embodiments, R^3 is



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In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $O(R^{4a'})$. In some embodiments, $R^{4a'}$ is H.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $O(R^{4a'})$. In some embodiments, $R^{4a'}$ is H.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

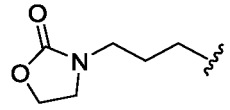
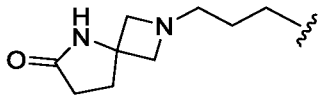
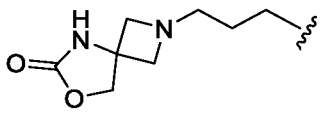
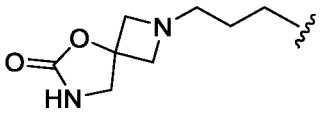
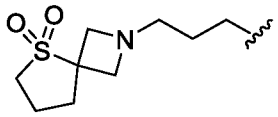
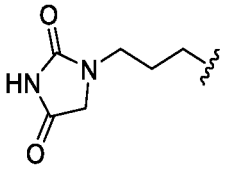
In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo. In some embodiments, R^3 is , , , , , or .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo.

In some embodiments, R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

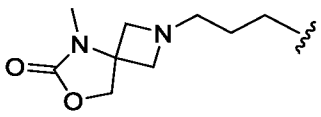
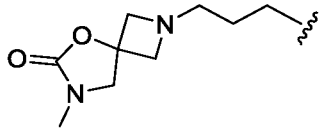
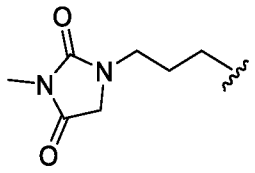
In some embodiments, R^3 is C_1-C_3 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl. In some embodiments, R^3 is


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In some embodiments, R^3 is isopropyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is optionally substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more oxo and one or more C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $O(R^{4a'})$ or C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$. In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted

with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

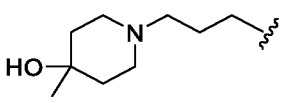
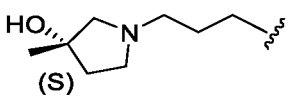
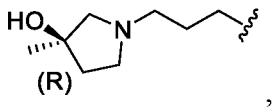
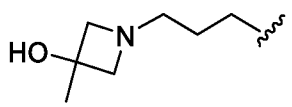
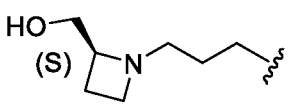
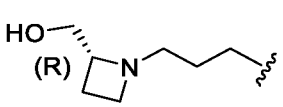
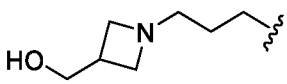
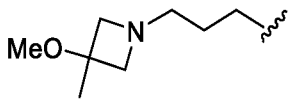
In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more O($R^{4a'}$) or C_1-C_6 alkyl that is optionally substituted with O(R^{4a}). In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, R^3 is , , , , , , , , or .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $O(R^{4a'})$ or C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$. In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $O(R^{4a'})$ or C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$. In some embodiments, R^{4a} and $R^{4a'}$ are each independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

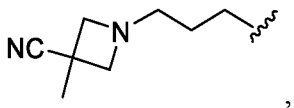
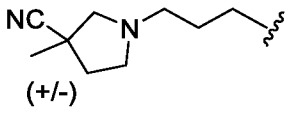
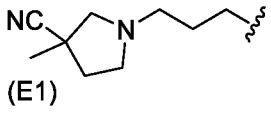
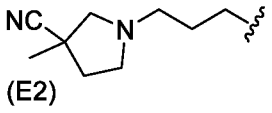
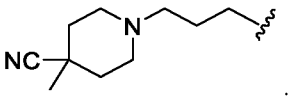
In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with

one or more -CN or C_1-C_6 alkyl. In some embodiments, R^3 is , , , , or .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more -CN or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

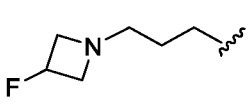
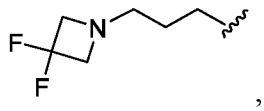
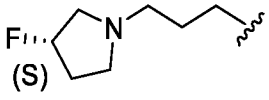
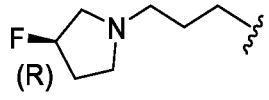
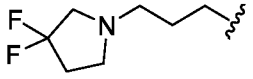
In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with

one or more halo. In some embodiments, R^3 is  ,  ,  ,  , or  .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more halo.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

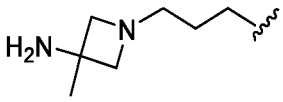
In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$

and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is 

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In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one or more $N(R^{4a'})(R^{4b'})$ and one or more C_1-C_6 alkyl. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

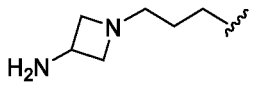
In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is



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In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

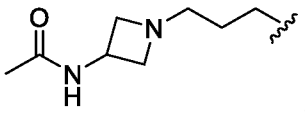
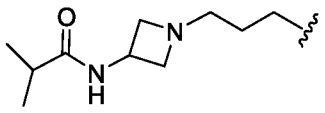
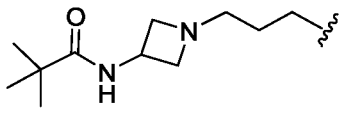
In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6

alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is


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In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

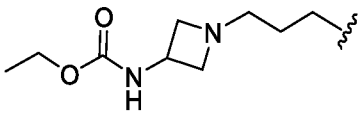
In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

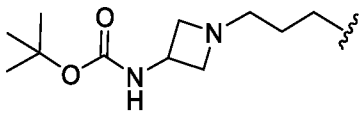
In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with

one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 is



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In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $N(R^{4a'})C(O)O(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

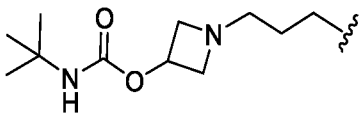
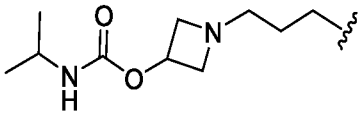
In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is , or .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl that is optionally substituted with one $OC(O)N(R^{4a'})(R^{4b'})$. In some embodiments, each R^{4a} and R^{4b} is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

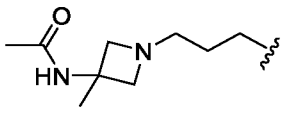
In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl. In some embodiments, R^3 is 

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In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with one C_1-C_6 alkyl and one $N(R^{4a'})C(O)(R^{4b'})$. In some embodiments, each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-alkyl further substituted with an 8- to 11-membered spirocycle with 0-3 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_2-alkyl further substituted with an 8- to 11-membered spirocycle with 0-3 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_3-alkyl further substituted with an 8- to 11-membered spirocycle with 0-3 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_1-alkyl further substituted with an 8- to 9-membered spirocycle with 0-2 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_2-alkyl further substituted with an 8- to 9-membered spirocycle with 0-2 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_3-alkyl further substituted with an 8- to 9-membered spirocycle with 0-2 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_1-alkyl further substituted with an 8- to 9-membered spirocycle with 1-2 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_2-alkyl further substituted with an 8- to 9-membered spirocycle with 1-2 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_3-alkyl further substituted with an 8- to 9-membered spirocycle with 1-2 heteroatoms selected from N, O, and S.

In some embodiments, R^3 is C_1-alkyl further substituted with an 8- to 11-membered spirocycle with 0-3 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_2-alkyl further substituted with an 8- to 11-membered spirocycle with 0-3 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_3-alkyl further substituted with an 8- to 11-membered spirocycle with 0-3 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_1-alkyl further substituted with an 8- to 9-membered spirocycle with 0-2 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

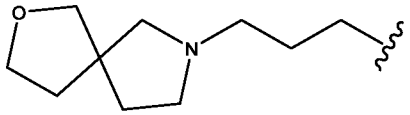
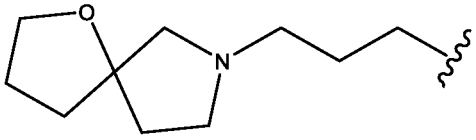
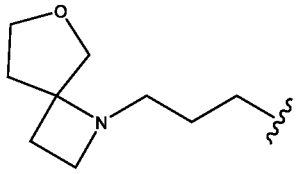
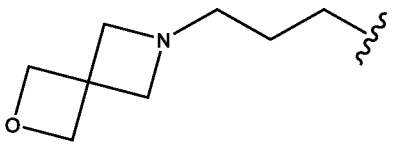
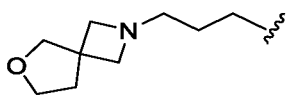
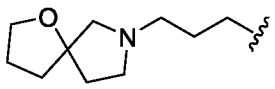
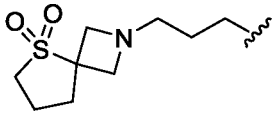
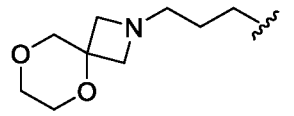
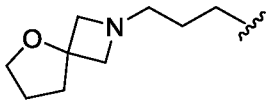
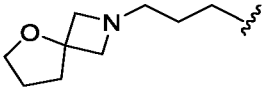
In some embodiments, R^3 is C_2-alkyl further substituted with an 8- to 9-membered spirocycle with 0-2 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_3-alkyl further substituted with an 8- to 9-membered spirocycle with 0-2 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_1-alkyl further substituted with an 8- to 9-membered spirocycle with 1-2 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_2-alkyl further substituted with an 8- to 9-membered spirocycle with 1-2 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is C_3-alkyl further substituted with an 8- to 9-membered spirocycle with 1-2 heteroatoms selected from N, O, and S, wherein the ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$.

In some embodiments, R^3 is , , , , , , , , , , or .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl.

In some embodiments, R^3 is C_1-C_6 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is C_1-C_5 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

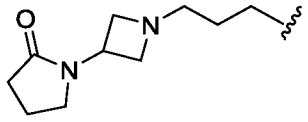
In some embodiments, R^3 is C_1-C_4 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is C_1-C_3 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is C_1-C_2 alkyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is methyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is ethyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is propyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo. In some embodiments, R^3 is .

In some embodiments, R^3 is isopropyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^3 is butyl that is substituted with one or more R^{3a}, wherein R^{3a} is 3- to 12-membered heterocyclyl that is substituted with 3- to 12-membered heterocyclyl that is substituted with oxo.

In some embodiments, R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$.

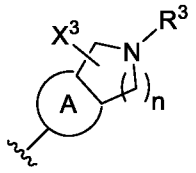
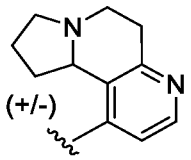
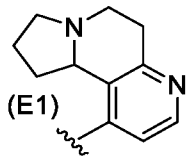
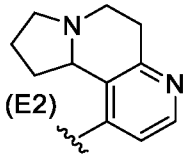
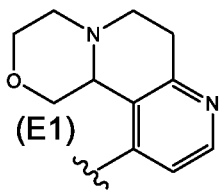
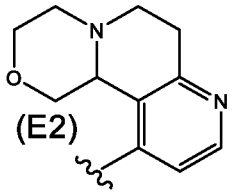
In some embodiments, R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more 3- to 12-membered heterocyclyl that is optionally substituted with oxo.

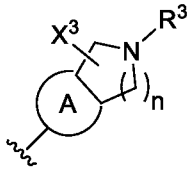
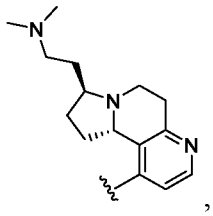
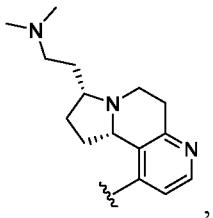
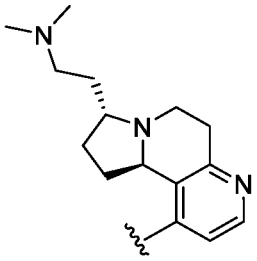
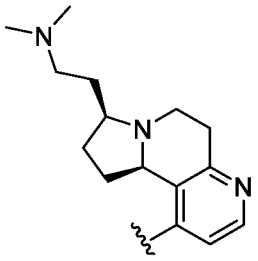
In some embodiments, R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a},

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-

C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl. In some embodiments, R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected.

In some embodiments,  is , , , , or .

In some embodiments,  is , , , or .

In some embodiments, n is 1.

In some embodiments, n is 2.

In some embodiments, n is 3.

In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O.

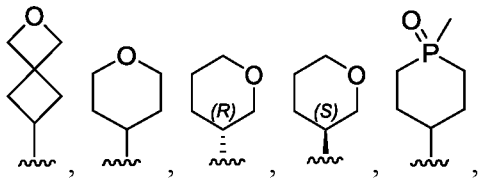
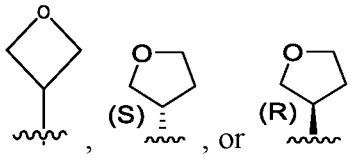
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2$-phenyl, R^2 is isopropyl, and Z is O.

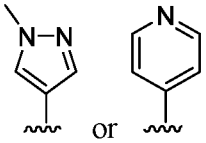
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O.

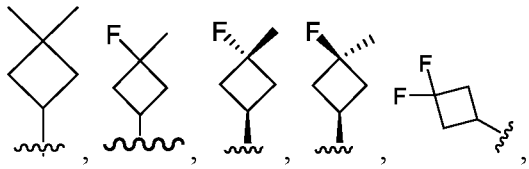
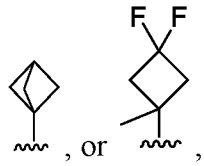
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O.

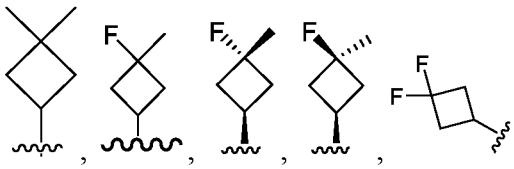
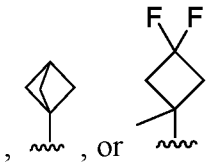
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, and Z is O.

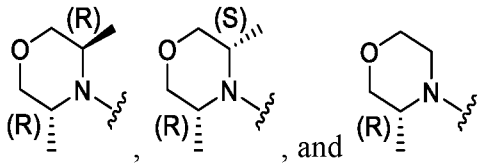
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and Z is O.

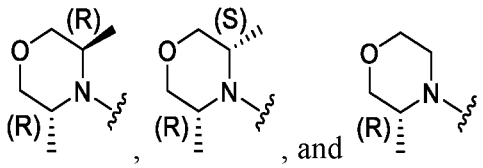
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, and Z is O.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and Z is O.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:



In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:



In some embodiments, W is CH, Y is N, and Z is CH_2.

In some embodiments, W is CH, Y is N, R^1 is ethyl, and Z is CH_2.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, and Z is CH_2.

In some embodiments, W is CH, Y is N, R^2 is isopropyl, and Z is CH_2.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is CH_2.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Z is CH_2.

In some embodiments, W is CH, Y is N, and Z is NH.

In some embodiments, W is CH, Y is N, R^1 is ethyl, and Z is NH.

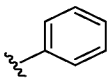
In some embodiments, W is CH, Y is N, R^1 is isopropyl, and Z is NH.

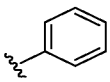
In some embodiments, W is CH, Y is N, R^2 is isopropyl, and Z is NH.

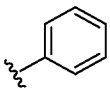
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is NH.

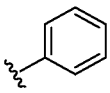
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Z is NH.

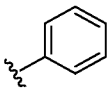
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

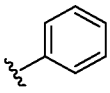
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

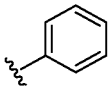
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

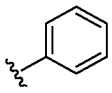
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

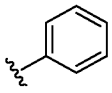
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

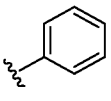
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

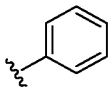
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

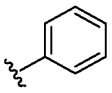
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

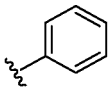
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

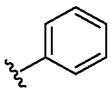
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

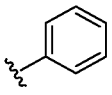
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

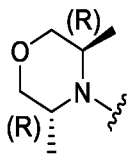
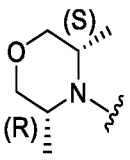
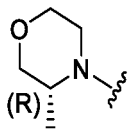
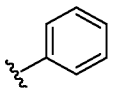
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

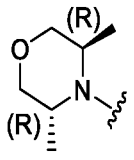
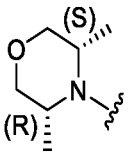
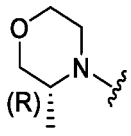
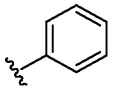
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

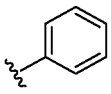
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

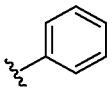
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

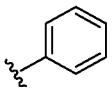
, , and , and Ring A is .

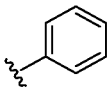
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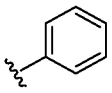
, , and , and Ring A is .

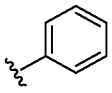
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

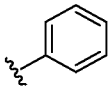
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

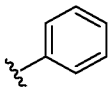
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

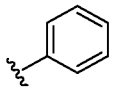
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

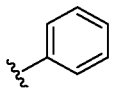
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

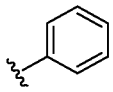
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

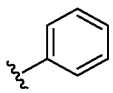
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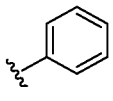
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

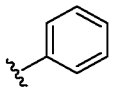
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and Ring A is .

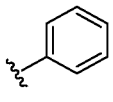
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and Ring A is .

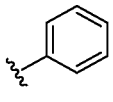
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and Ring A is .

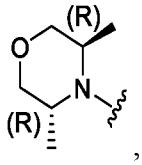
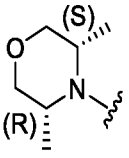
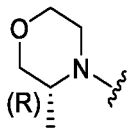
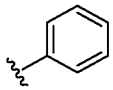
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and Ring A is .

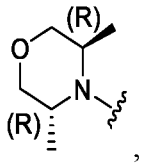
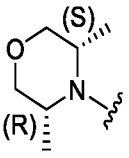
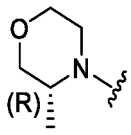
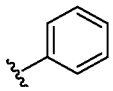
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

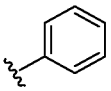
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

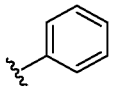
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

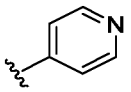
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

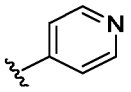
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from: , , and , Z is O, and Ring A is .

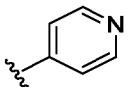
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from: , , and , Z is O, and Ring A is .

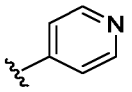
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, and Ring A is .

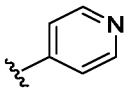
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, and Ring A is .

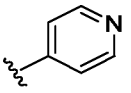
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

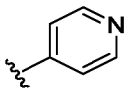
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

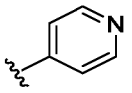
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

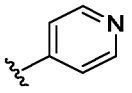
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Ring A is .

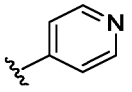
In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, and Ring A is .

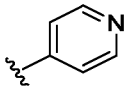
In some embodiments, W is CH, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, and Ring A is .

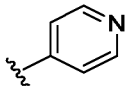
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, and Ring A is .

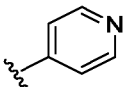
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

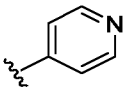
In some embodiments, W is N, Y is CH, R^1 is isopropyl. R^2 is isopropyl, and Ring A is .

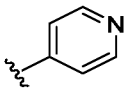
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

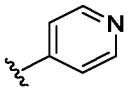
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Ring A is .

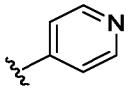
In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, and Ring A is .

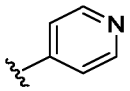
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

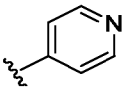
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

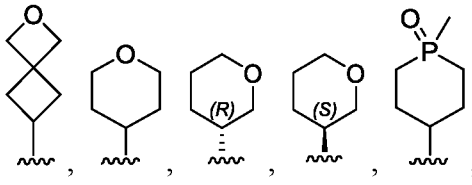
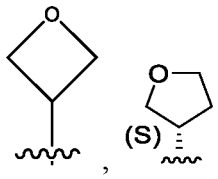
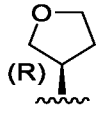
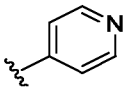
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Ring A is .

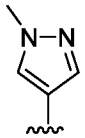
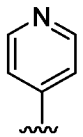
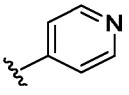
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

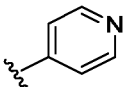
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

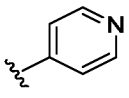
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

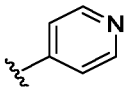
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Ring A is .

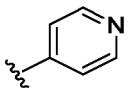
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and Ring A is .

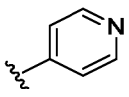
In some embodiments, W is CH, Y is N, R^1 is  or . R^2 is isopropyl, and Ring A is .

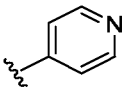
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and Ring A is .

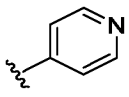
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and Ring A is .

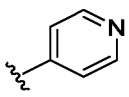
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CN$, R^2 is isopropyl, and Ring A is .

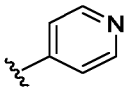
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, and Ring A is .

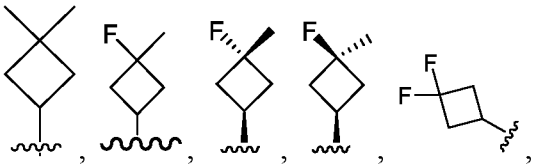
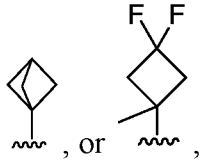
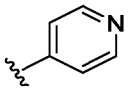
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, and Ring A is .

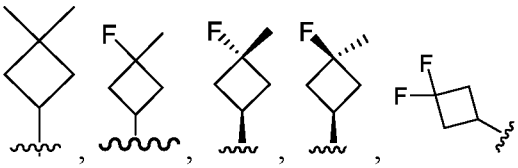
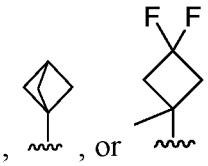
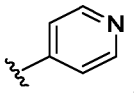
In some embodiments, W is N, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, and Ring A is .

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, and Ring A is .

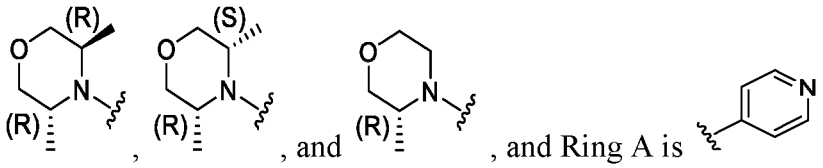
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, and Ring A is .

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, and Ring A is .

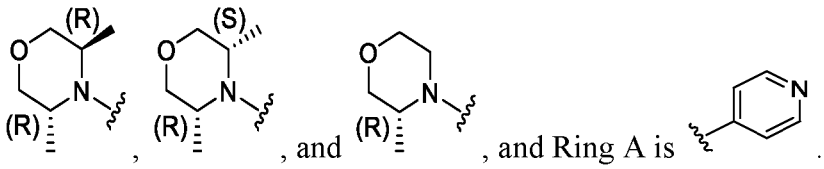
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, and Ring A is .

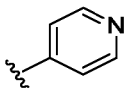
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and Ring A is .

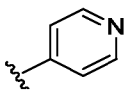
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

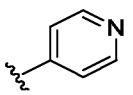


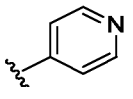
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

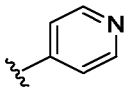


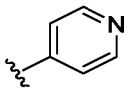
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

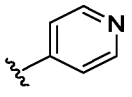
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

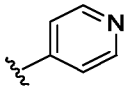
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

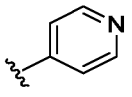
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and Ring A is .

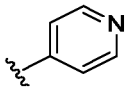
In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, Z is O, and Ring A is .

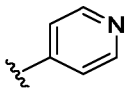
In some embodiments, W is CH, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, and Ring A is .

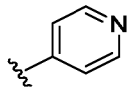
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, and Ring A is .

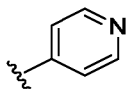
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

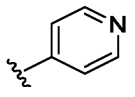
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

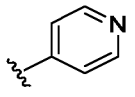
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

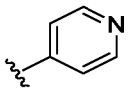
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is .

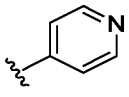
In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and Ring A is .

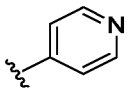
In some embodiments, W is N, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and Ring A is .

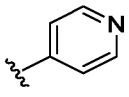
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and Ring A is .

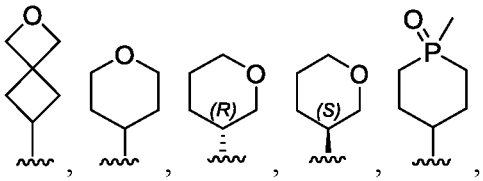
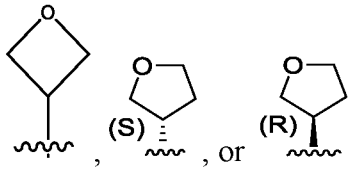
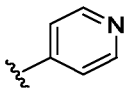
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and Ring A is .

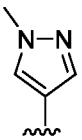
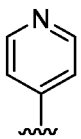
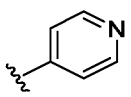
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

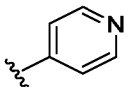
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

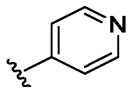
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

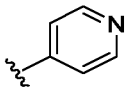
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and Ring A is .

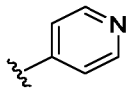
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and Ring A is .

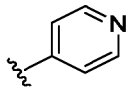
In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Z is O, and Ring A is .

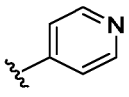
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and Ring A is .

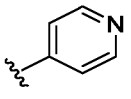
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and Ring A is .

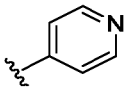
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Z is O, and Ring A is .

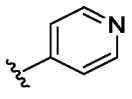
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, and Ring A is .

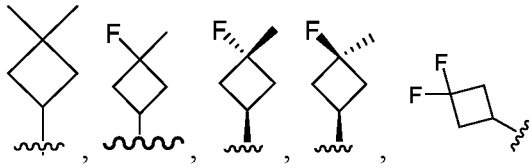
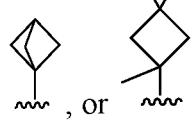
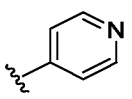
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, and Ring A is .

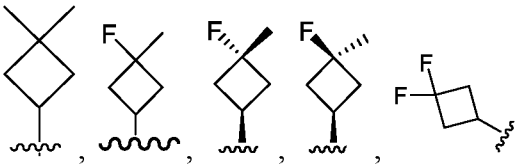
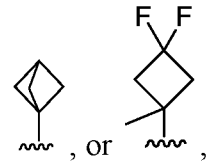
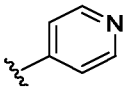
In some embodiments, W is N, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, and Ring A is .

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, and Ring A is .

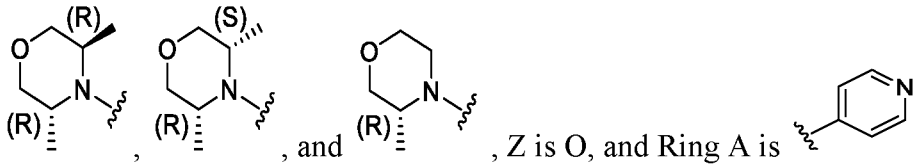
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, Z is O, and Ring A is .

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, Z is O, and Ring A is .

In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and Ring A is .

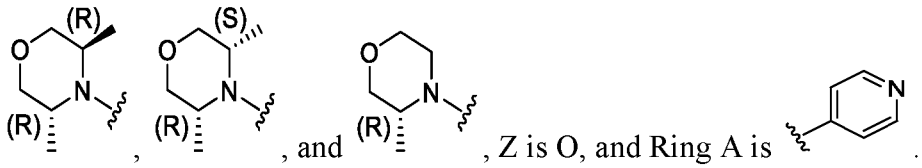
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and Ring A is .

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

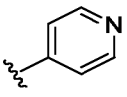


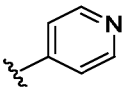
, Z is O, and Ring A is .

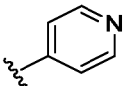
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

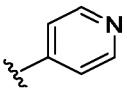


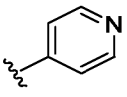
, Z is O, and Ring A is .

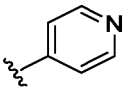
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, and Ring A is .

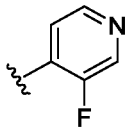
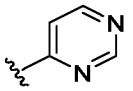
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, and Ring A is .

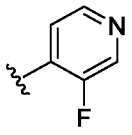
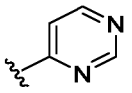
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, and Ring A is .

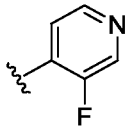
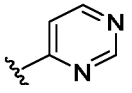
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, and Ring A is .

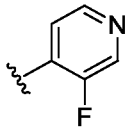
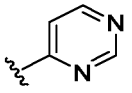
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, and Ring A is .

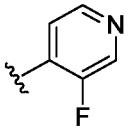
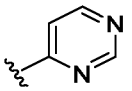
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, and Ring A is .

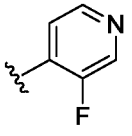
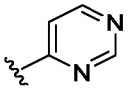
In some embodiments, W is CH, Y is N, and Ring A is  , or  .

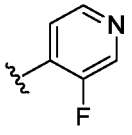
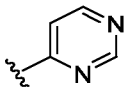
In some embodiments, W is CH, Y is N, R^1 is ethyl, and Ring A is  , or  .

In some embodiments, W is CH, Y is N, R^1 is isopropyl, and Ring A is  , or  .

In some embodiments, W is CH, Y is N, R^2 is isopropyl, and Ring A is  , or  .

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Ring A is  , or  .

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Ring A is  , or  .

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and Ring A is  , or  .

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, and Z is O, and X^3 is H.

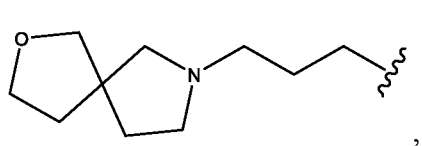
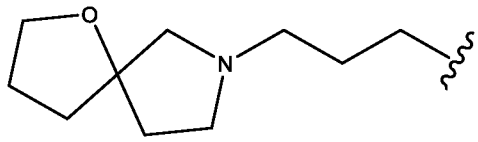
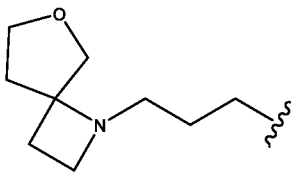
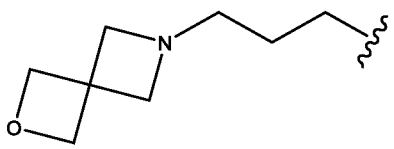
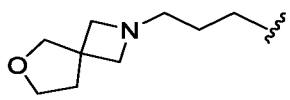
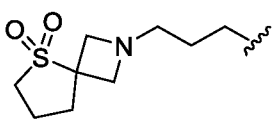
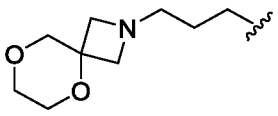
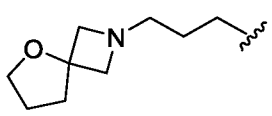
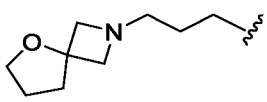
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, Z is O, and X^3 is H.

In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is , , , , , , , , or .

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O, and X^3 is H.

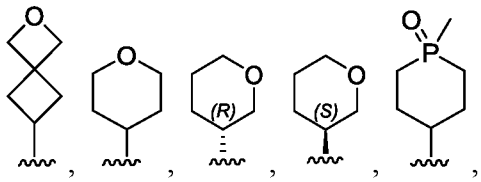
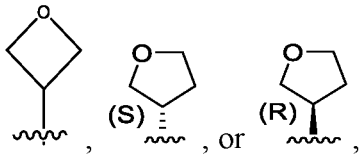
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and Z is O, and X^3 is H.

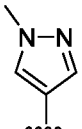
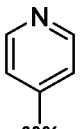
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O, and X^3 is H.

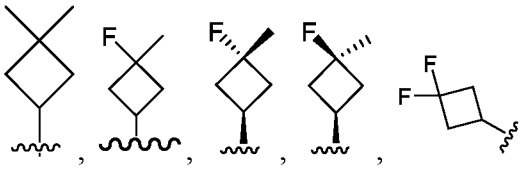
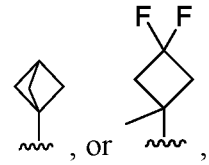
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and Z is O, and X^3 is H.

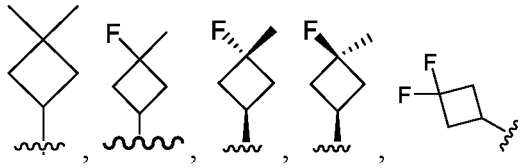
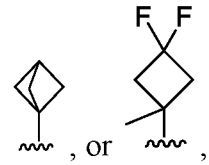
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, and Z is O, and X^3 is H.

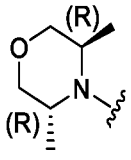
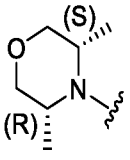
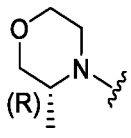
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and Z is O, and X^3 is H.

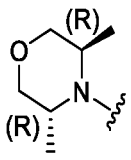
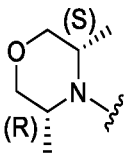
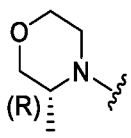
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and Z is O, and X^3 is H.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, , and , and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

, , and , and Z is O, and X^3 is H.

In some embodiments, W is CH, Y is N, Z is CH_2, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, Z is CH_2, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, Z is CH_2, and X^3 is H.

In some embodiments, W is CH, Y is N, R^2 is isopropyl, Z is CH_2, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and Z is CH_2, and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, and X^3 is H.

In some embodiments, W is CH, Y is N, Z is NH, and X^3 is H.

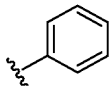
In some embodiments, W is CH, Y is N, R^1 is ethyl, Z is NH, and X^3 is H.

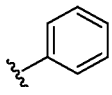
In some embodiments, W is CH, Y is N, R^1 is isopropyl, Z is NH, and X^3 is H.

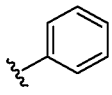
In some embodiments, W is CH, Y is N, R^2 is isopropyl, Z is NH, and X^3 is H.

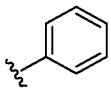
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, and X^3 is H.

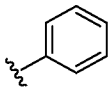
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, and X^3 is H.

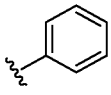
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

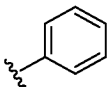
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

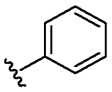
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

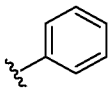
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

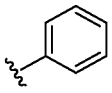
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

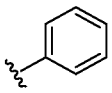
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

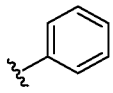
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

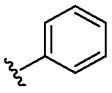
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

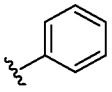
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and X^3 is H.

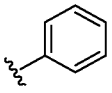
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and X^3 is H.

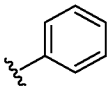
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and X^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and X^3 is H.

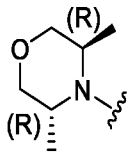
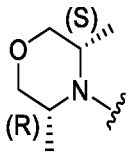
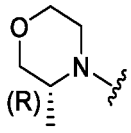
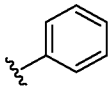
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

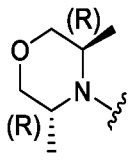
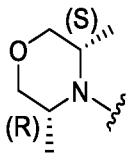
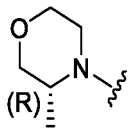
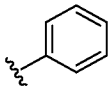
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

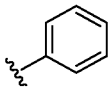
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

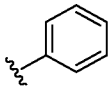
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

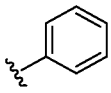



, Ring A is , and X^3 is H.

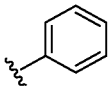
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

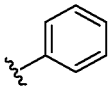



, Ring A is , and X^3 is H.

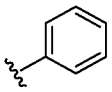
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

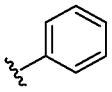
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

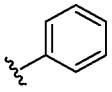
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

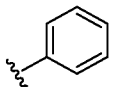
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

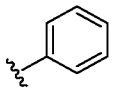
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

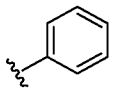
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

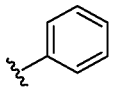
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

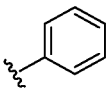
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

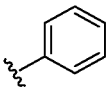
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

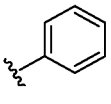
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

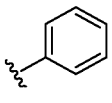
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

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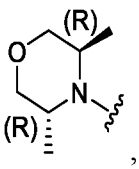
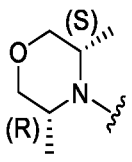
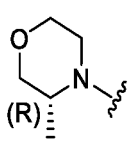
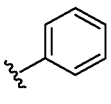
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

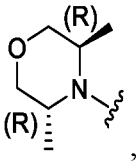
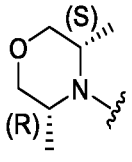
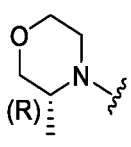
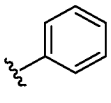
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

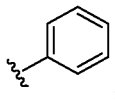
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

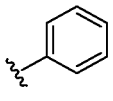
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

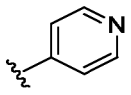
, , and , Z is O, Ring A is , and X^3 is H.

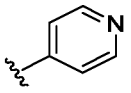
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

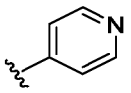
, , and , Z is O, Ring A is , and X^3 is H.

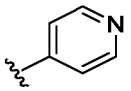
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, Ring A is , and X^3 is H.

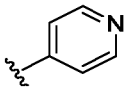
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, Ring A is , and X^3 is H.

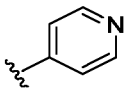
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

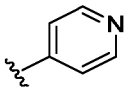
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

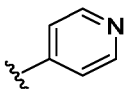
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

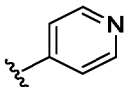
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is H.

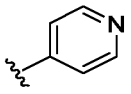
In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, Ring A is , and X^3 is H.

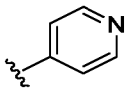
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

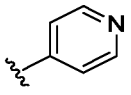
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

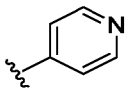
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

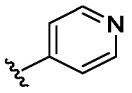
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is H.

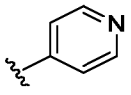
In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , and X^3 is H.

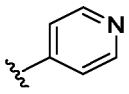
In some embodiments, W is N, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , and X^3 is H.

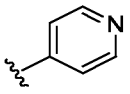
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , and X^3 is H.

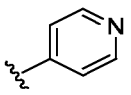
In some embodiments, W is CH, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , and X^3 is H.

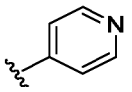
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Ring A is , and X^3 is H.

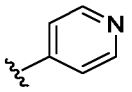
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Ring A is , and X^3 is H.

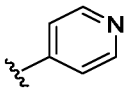
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Ring A is , and X^3 is H.

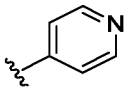
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Ring A is , and X^3 is H.

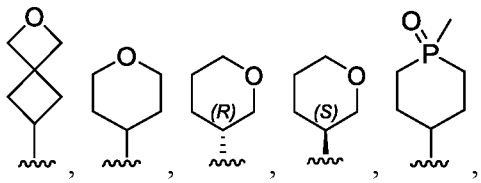
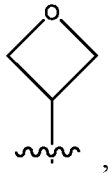
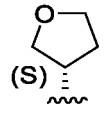
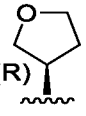
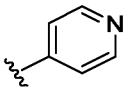
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Ring A is , and X^3 is H.

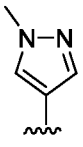
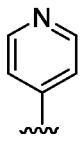
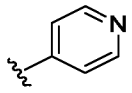
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

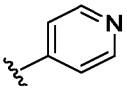
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

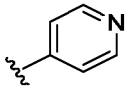
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

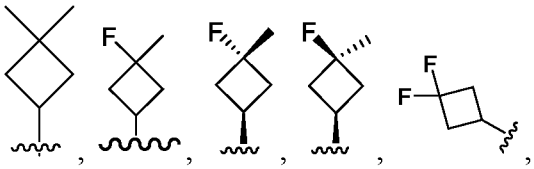
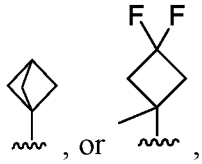
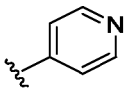
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is H.

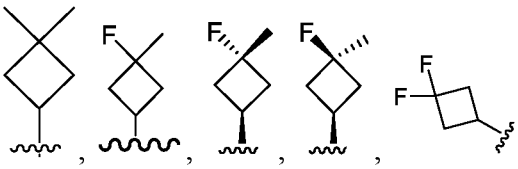
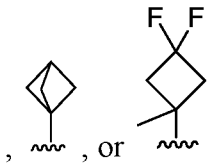
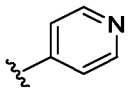
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, Ring A is , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Ring A is , and X^3 is H.

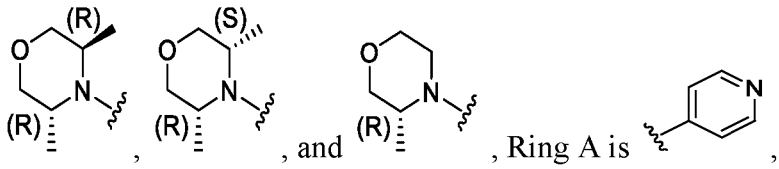
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and X^3 is H.

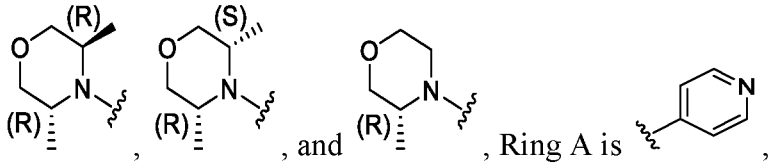
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Ring A is , and X^3 is H.

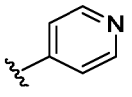
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Ring A is , and X^3 is H.

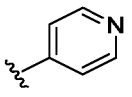
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

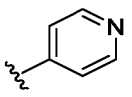
, and , Ring A is , and X^3 is H.

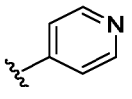
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

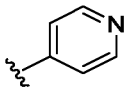
, and , Ring A is , and X^3 is H.

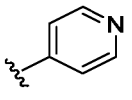
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

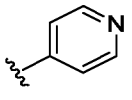
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is $-CH_2-O-CH_2-CHF_2$.

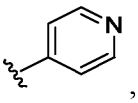
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

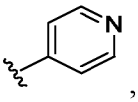
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

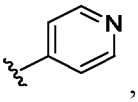
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

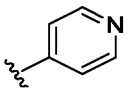
In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

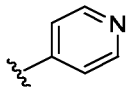
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

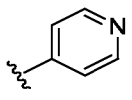
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

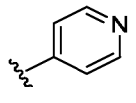
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

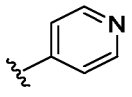
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

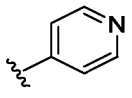
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

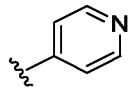
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

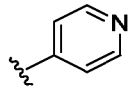
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is  , and X^3 is H.

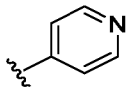
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

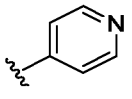
In some embodiments, W is N, Y is N, R^1 is $-CH_2$-phenyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

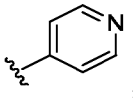
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CN$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

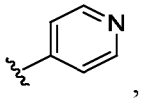
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

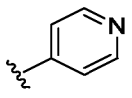
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

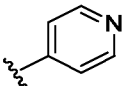
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

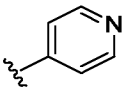
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

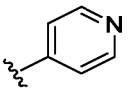
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

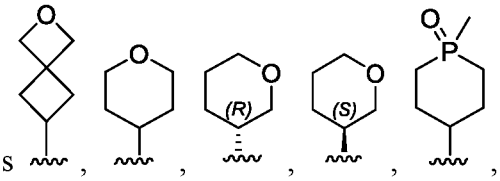
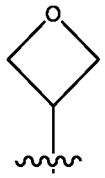
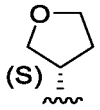
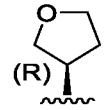
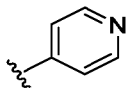
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

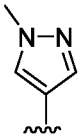
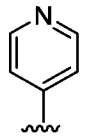
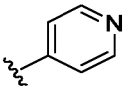
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

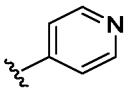
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

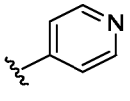
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

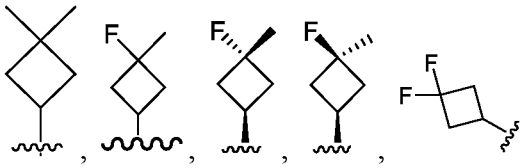
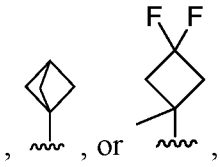
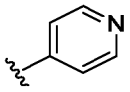
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

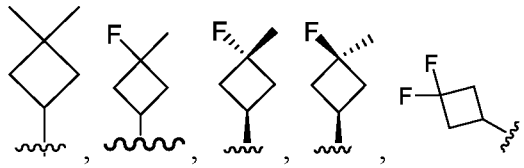
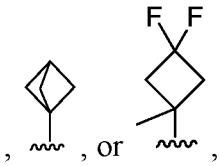
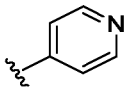
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

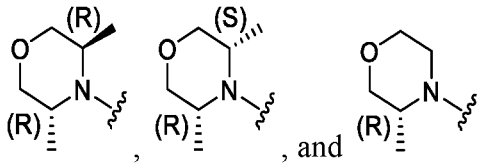
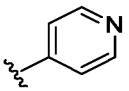
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

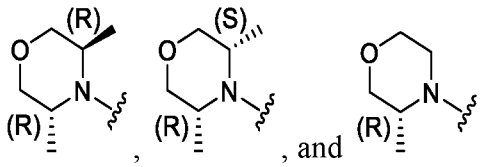
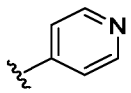
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

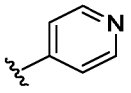
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is H.

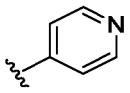
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

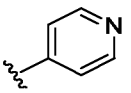
, and , Z is O, Ring A is , and X^3 is H.

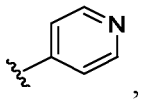
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

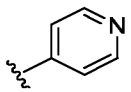
, and , Z is O, Ring A is , and X^3 is H.

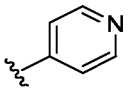
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is , and X^3 is H.

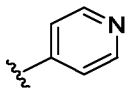
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is , and X^3 is H.

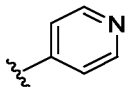
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, Ring A is , and X^3 is H.

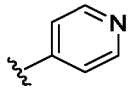
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, Ring A is , and X^3 is H.

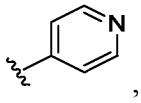
In some embodiments, W is CH, Y is N, Z is NH, Ring A is , and X^3 is H.

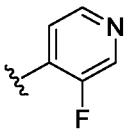
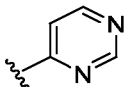
In some embodiments, W is CH, Y is N, R^1 is ethyl, Z is NH, Ring A is , and X^3 is H.

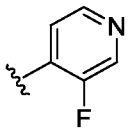
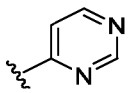
In some embodiments, W is CH, Y is N, R^1 is isopropyl, Z is NH, Ring A is , and X^3 is H.

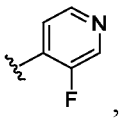
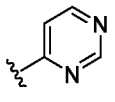
In some embodiments, W is CH, Y is N, R^2 is isopropyl, Z is NH, Ring A is , and X^3 is H.

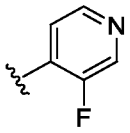
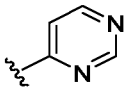
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, Ring A is , and X^3 is H.

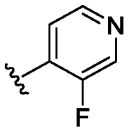
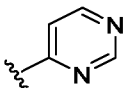
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, Ring A is , and X^3 is H.

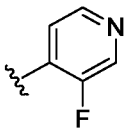
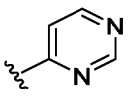
In some embodiments, W is CH, Y is N, Ring A is , or , and X^3 is H.

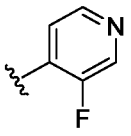
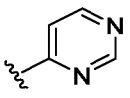
In some embodiments, W is CH, Y is N, R^1 is ethyl, Ring A is , or , and X^3 is H.

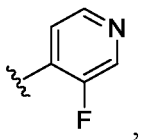
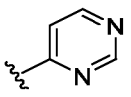
In some embodiments, W is CH, Y is N, R^1 is isopropyl, Ring A is , or , and X^3 is H.

In some embodiments, W is CH, Y is N, R^2 is isopropyl, Ring A is , or , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , or , and X^3 is H.

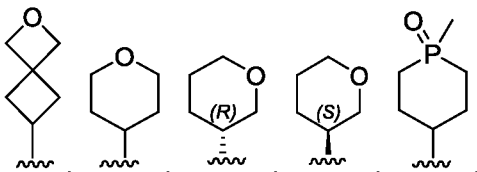
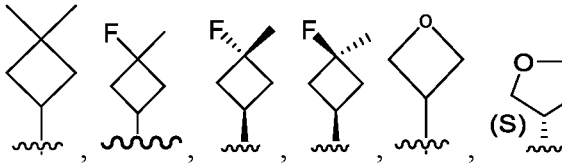
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , or , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , or , and X^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , or , and X^3 is H.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is , , and X^3 is hydrogen.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

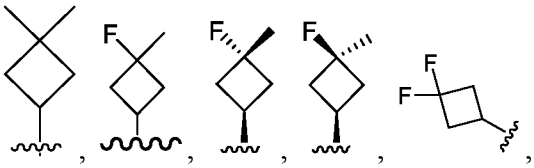
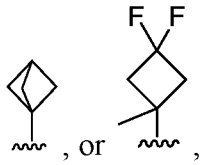
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

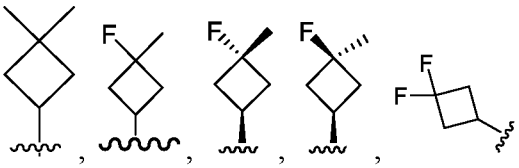
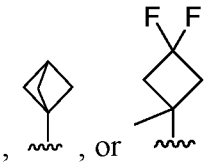
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl and R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and X^3 is -CH_2-O-CH_2-CHF_2.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

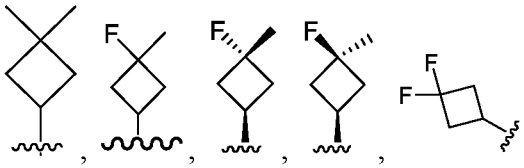
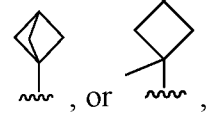
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

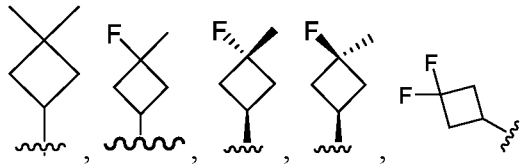
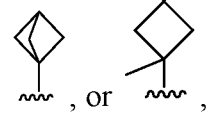
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

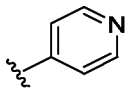
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

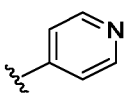
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

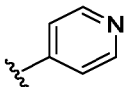
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

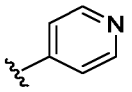
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

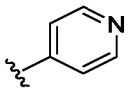
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and X^3 is methyl, ethyl, or isopropyl.

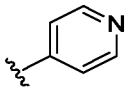
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

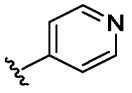
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

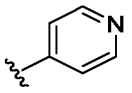
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

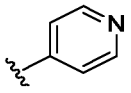
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

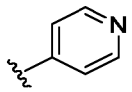
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

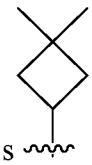
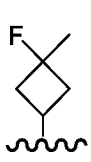
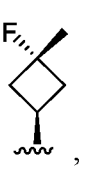
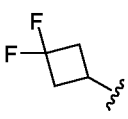
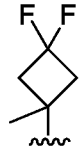
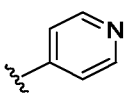
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

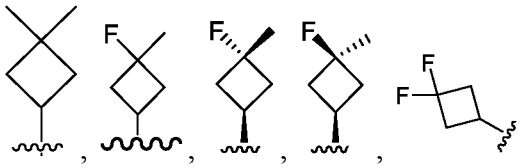
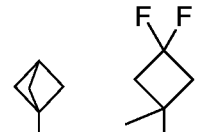
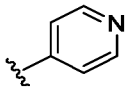
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

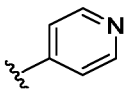
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

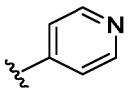
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

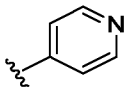
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

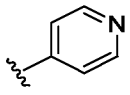
In some embodiments, W is N, Y is N, R^1 is , , , , , , or , R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

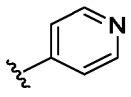
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

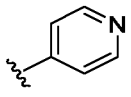
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

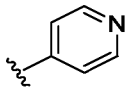
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

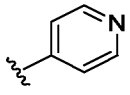
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

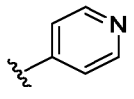
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

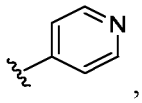
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

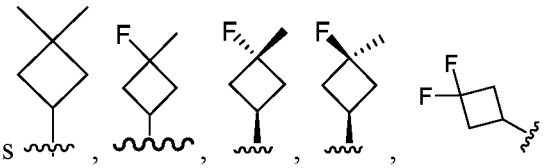
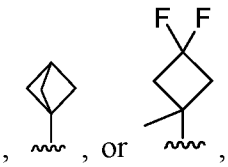
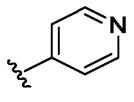
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

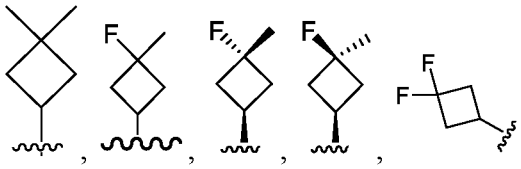
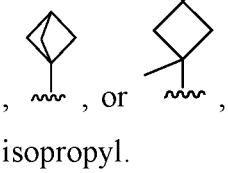
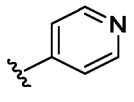
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

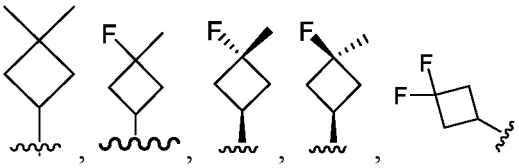
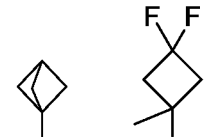
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and X^3 is -CH_2(OH), -CH_2-CH_2-CH_2(OH), -CH_2-OCH_3, -CH_2-CH_2-CH_2-O-CH_2-phenyl, -CH_2-CH_2-CH_2-C(=O)N(CH_3)$_2$, or -CH_2-CH_2-CH_2-N(CH_3)$_2$.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and X^3 is -CH_2(OH), -CH_2-CH_2-CH_2(OH), -CH_2-OCH_3, -CH_2-CH_2-CH_2-O-CH_2-phenyl, -CH_2-CH_2-CH_2-C(=O)N(CH_3)$_2$, or -CH_2-CH_2-CH_2-N(CH_3)$_2$.

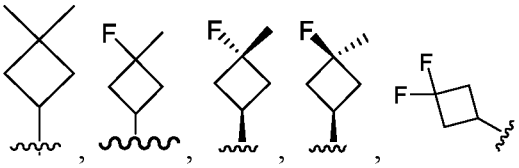
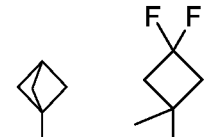
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl and R^2 is isopropyl, and X^3 is -CH_2(OH), -CH_2-CH_2-CH_2(OH), -CH_2-OCH_3, -CH_2-CH_2-CH_2-O-CH_2-phenyl, -CH_2-CH_2-CH_2-C(=O)N(CH_3)$_2$, or -CH_2-CH_2-CH_2-N(CH_3)$_2$.

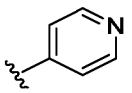
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

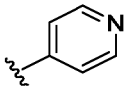
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

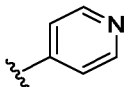
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

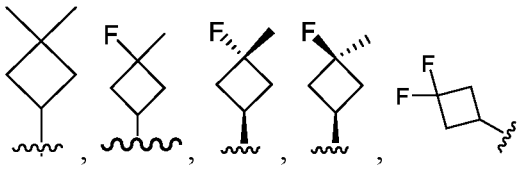
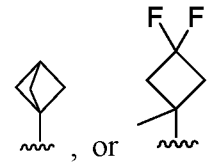
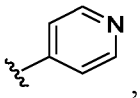
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

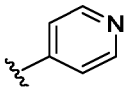
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

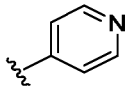
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

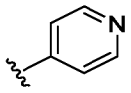
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

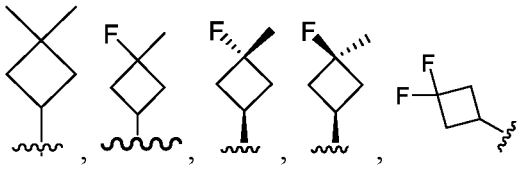
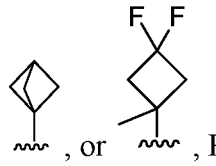
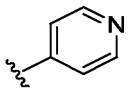
In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

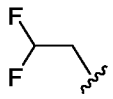
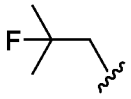
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and X^3 is $-CH_2(OH)$, $-CH_2-CH_2-$

$CH_2(OH)$, $-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-O-CH_2$-phenyl, $-CH_2-CH_2-CH_2-C(=O)N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_3)_2$.

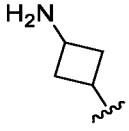
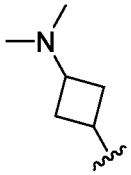
In any one of the proceeding embodiments, R^3 is selected from one or more of the following:

a. H;

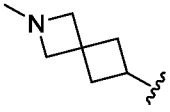
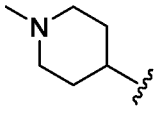
b. methyl, ethyl, or isopropyl;

c. , or ;

d. ;

e. , or ;

f. , or ;

g. , , or ;

h. $-CH_2-C(O)OH$, $-CH_2-CH_2-C(O)OH$, or $-CH_2-CH_2-OMe$;

i. $-CH_2-CH_2-CN$;

j. $-CH_2-CH_2-S(=O)_2Me$ or $-CH_2-CH_2-CH_2-S(=O)_2Me$;

k. $-CH_2-CH_2-NH(CH_3)$, $-CH_2-CH_2-CH_2-NH(CH_3)$, or $-CH_2-CH_2-CH_2-CH_2-NH(CH_3)$; or $-CH_2-CH_2-CH_2-CH_2-CH_2-NH(CH_3)$;

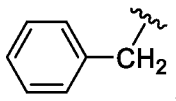
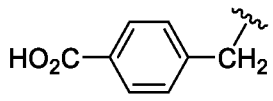
l. $-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$;

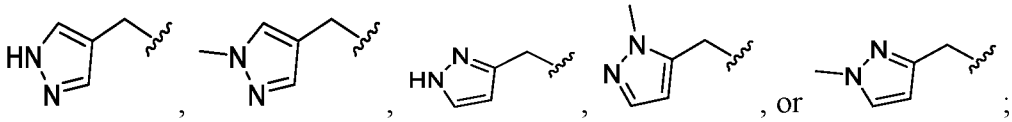
m. $-CH_2-CH_2-CH_2-N(CH_2-CH_3)_2$;

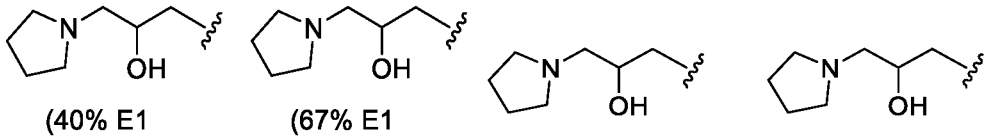
n. $-CH_2-CH_2-NH_2$, $-CH_2-CH_2-CH_2-NH_2$, or $-CH_2-CH_2-C(CH_3)_2(NH_2)$;

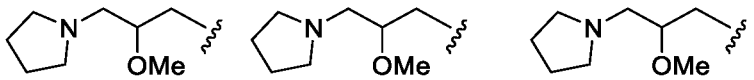
o. $-CH_2-CH_2-OH$, $-CH_2-CH_2-CH_2-OH$, $-CH_2-CH_2-C(CH_3)_2(OH)$, $-CH_2-C(CH_3)_2(OH)$, $-CH_2-C(CH_3)_2(OH)$, or $-CH_2-CH_2-C(CH_3)_2(OH)$;

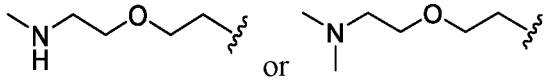
p. $-CH_2-C(O)OH$; or $-CH_2-CH_2-C(O)OH$;

q. , or ;

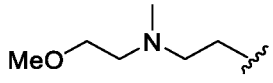
r. ;

s. 
(40% E1 60% E2), (67% E1 33% E2), (E1), or (E2);

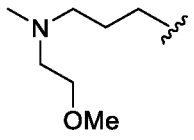
t. 
(E1), (+/-), or (E2);

u. ;

v. $-CH_2-CH_2-NH_2$, $-CH_2-CH_2-NH(CH_3)$, or $-CH_2-CH_2-N(CH_3)_2$;

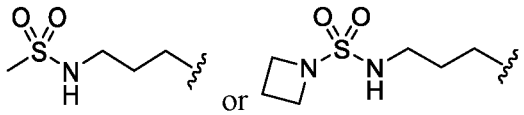
w. ;

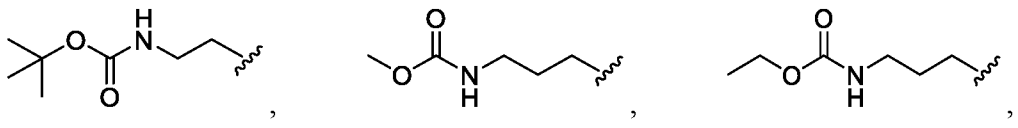
x. $-CH_2-CH_2-CH_2-NH_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_2-CH_3)_2$;

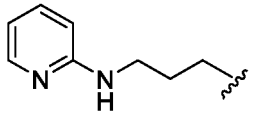
y. ;

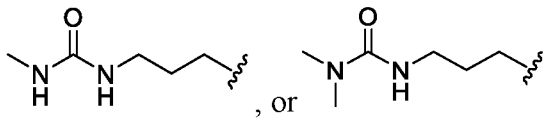
z. $-CH_2-CH_2-CH_2-CH_2-NH(CH_3)$, $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-C(CH_3)_2(NH_2)$;

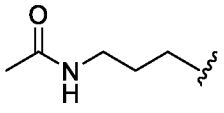
aa. $-CH_2-CH_2-CH_2-CH_2-CH_2-NH(CH_3)$, or $-CH_2-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$;

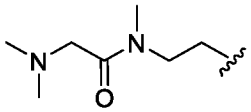
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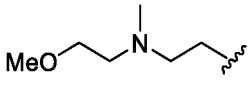
cc. ;

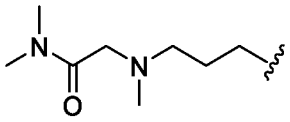
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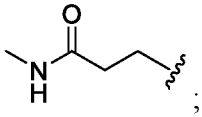
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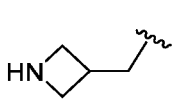
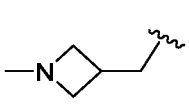
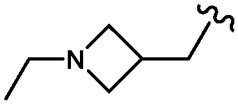
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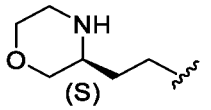
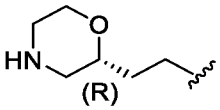
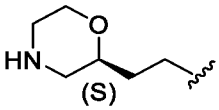
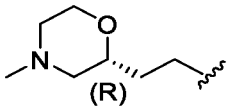
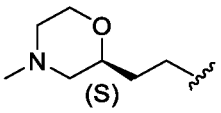
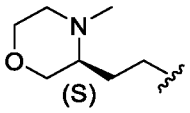
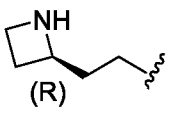
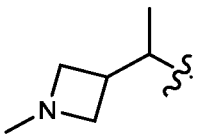
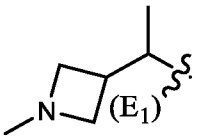
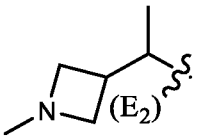
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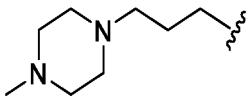
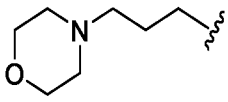
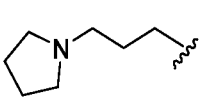
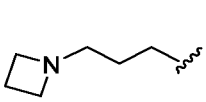
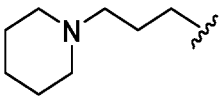
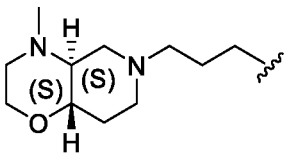
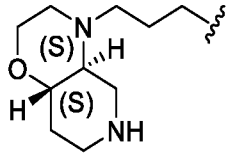
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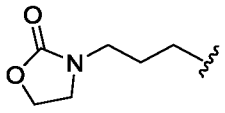
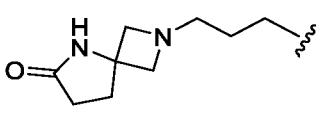
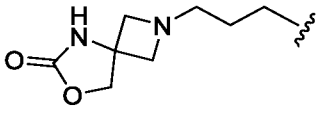
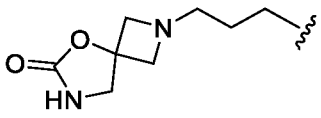
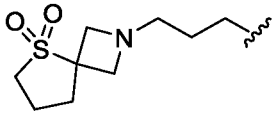
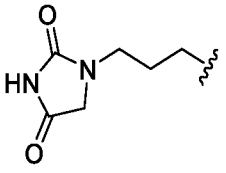
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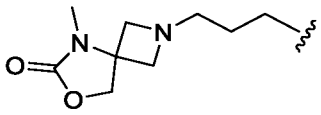
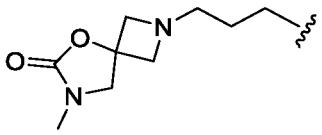
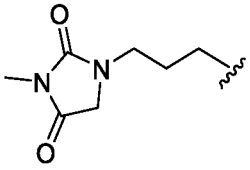
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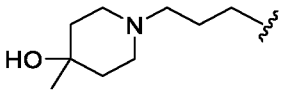
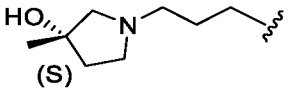
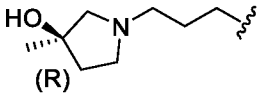
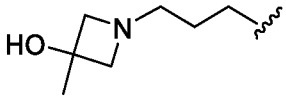
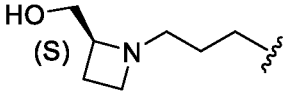
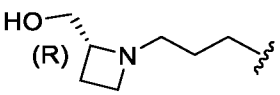
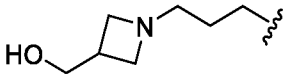
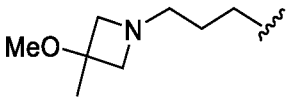
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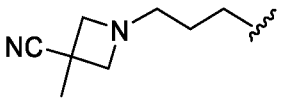
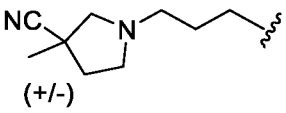
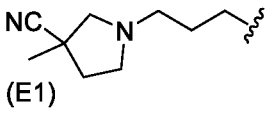
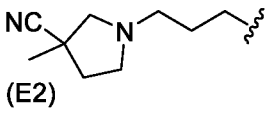
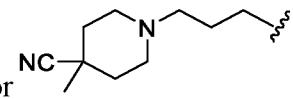










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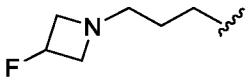
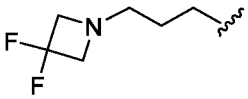
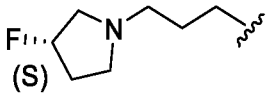
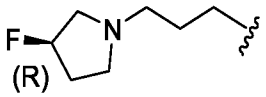
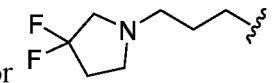
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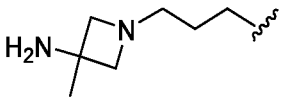
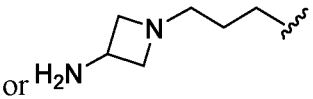
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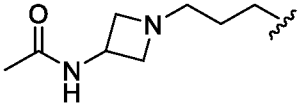
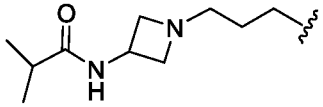
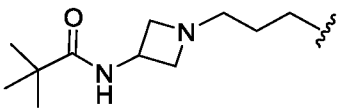
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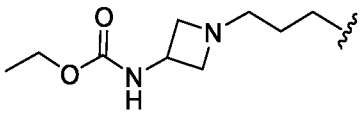
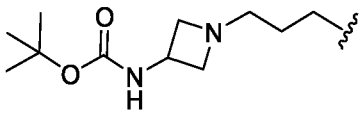
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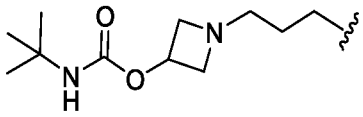
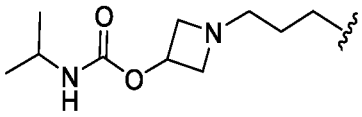
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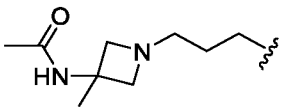
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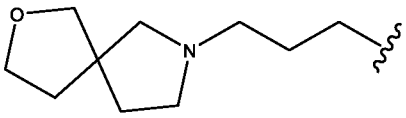
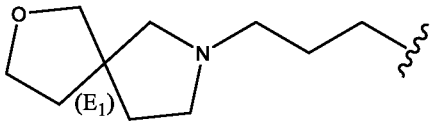
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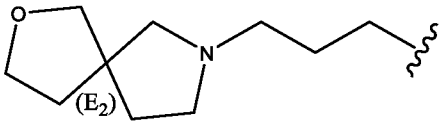
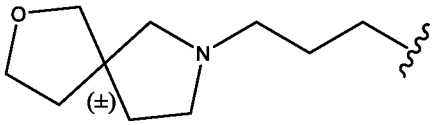
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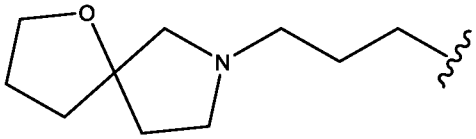
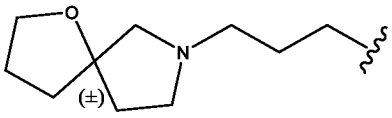
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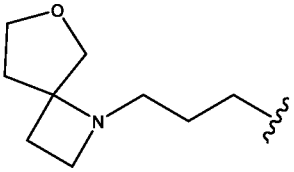
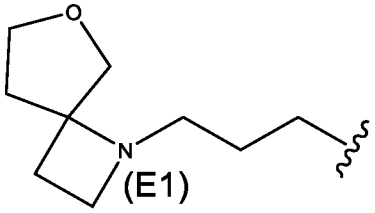
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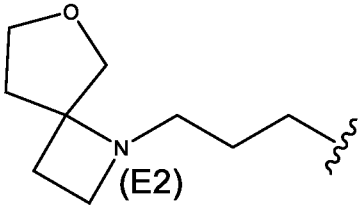
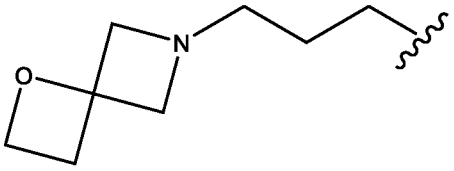
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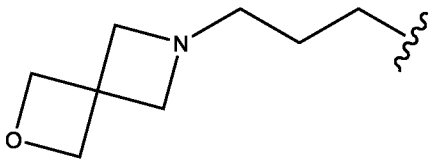
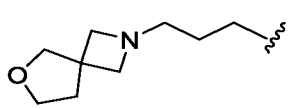
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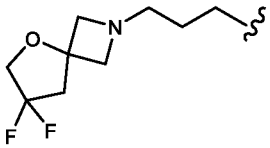
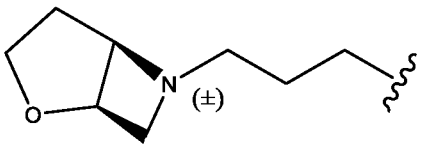
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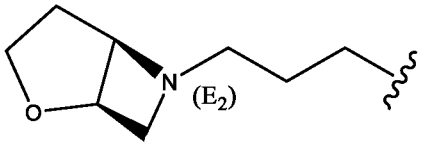
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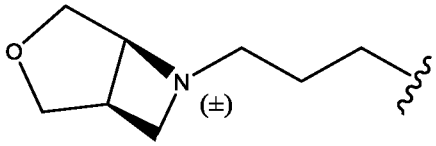
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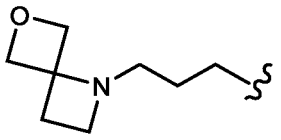
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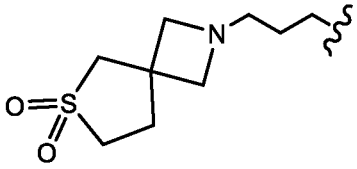
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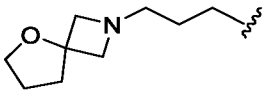
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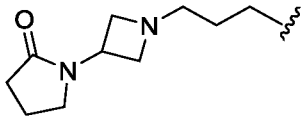
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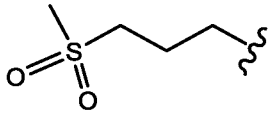
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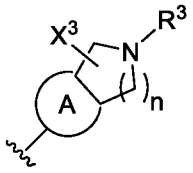
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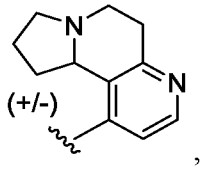
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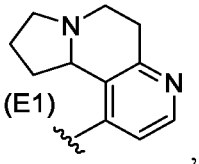
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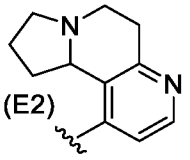
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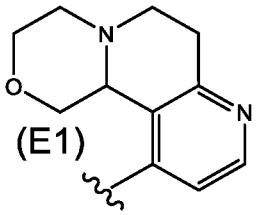
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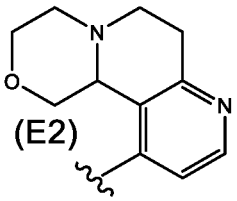
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In any one of the previous embodiments, wherein n is 1.

In any one of the previous embodiments, wherein n is 2.

In any one of the previous embodiments, wherein n is 3.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and R^3 is H.

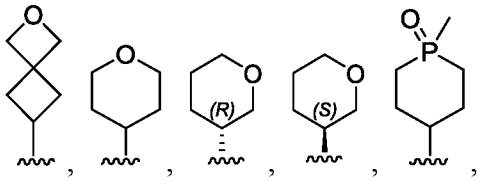
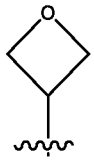
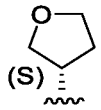
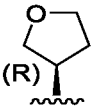
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, and R^3 is H.

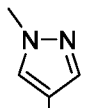
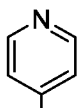
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, and R^3 is H.

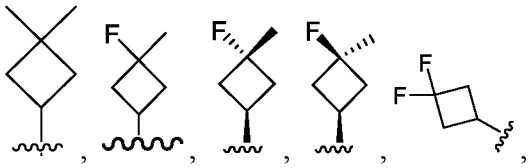
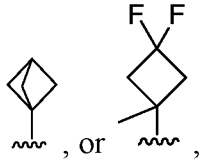
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, and R^3 is H.

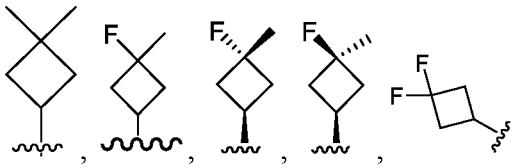
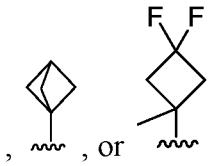
In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and R^3 is H.

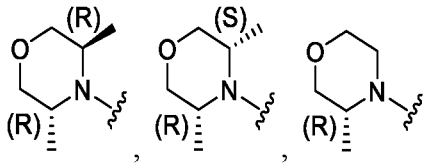
In some embodiments, W is N, Y is CH, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl and R^2 is isopropyl, and R^3 is H.

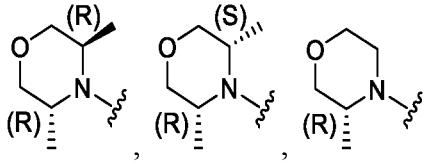
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, and R^3 is H

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

, and R^3 is H

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and R^3 is H.

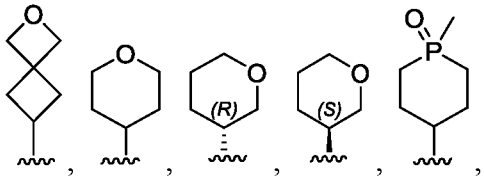
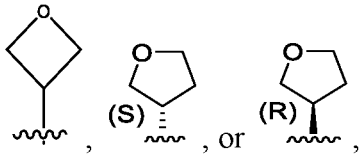
In some embodiments, W is CH, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Z is O, and R^3 is H.

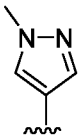
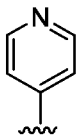
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and R^3 is H.

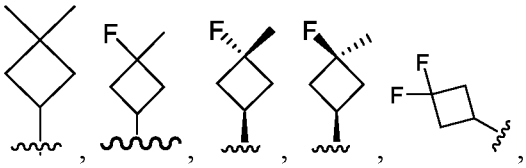
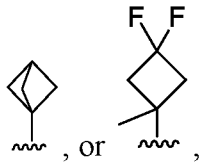
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, and R^3 is H.

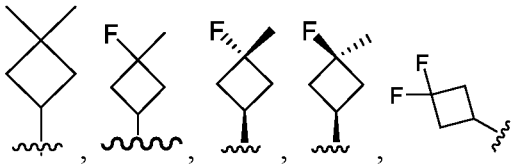
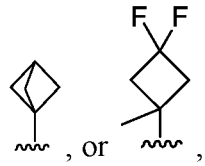
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Z is O, and R^3 is H.

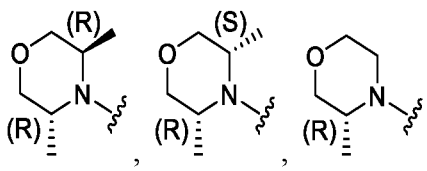
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, and R^3 is H.

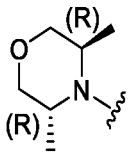
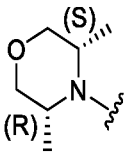
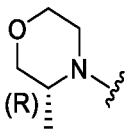
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:




, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, and R^3 is H.

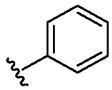
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, and R^3 is H.

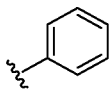
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, and R^3 is H.

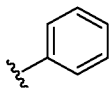
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, and R^3 is $-CH_3$.

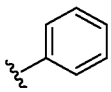
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, and R^3 is $-CH_3$.

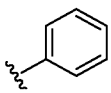
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Z is O, and R^3 is $-CH_3$.

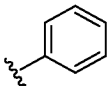
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

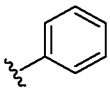
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

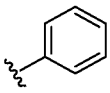
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

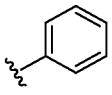
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

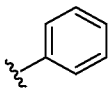
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

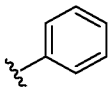
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

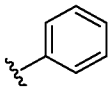
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

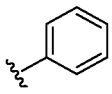
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

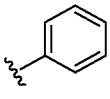
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is H.

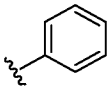
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is H.

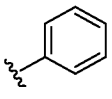
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is H.

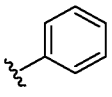
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is $-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$.

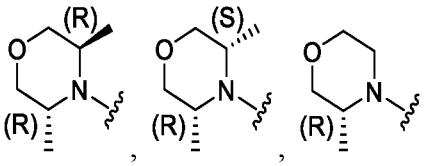
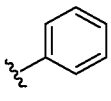
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

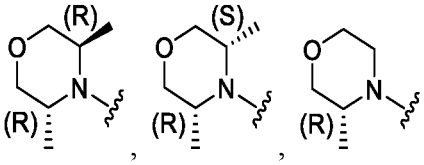
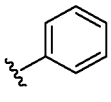
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

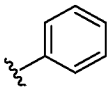
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

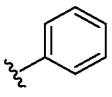
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

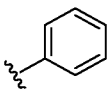
, Ring A is , and R^3 is H.

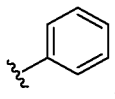
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

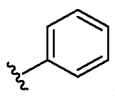
, Ring A is , and R^3 is H.

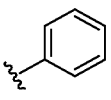
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

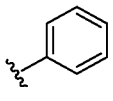
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

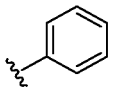
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

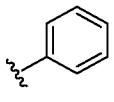
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

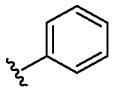
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

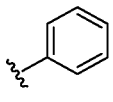
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

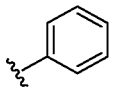
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

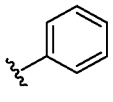
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

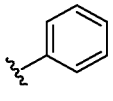
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

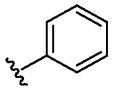
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

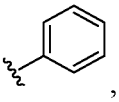
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

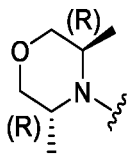
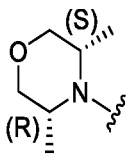
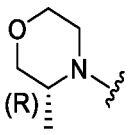
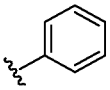
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

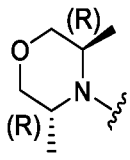
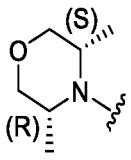
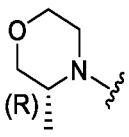
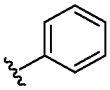
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

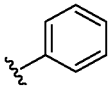
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

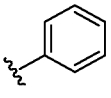
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

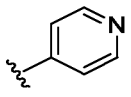



, Z is O, Ring A is , and R^3 is H.

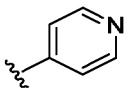
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

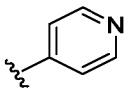



, Z is O, Ring A is , and R^3 is H.

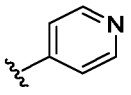
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, Ring A is , and R^3 is H.

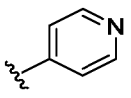
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, Ring A is , and R^3 is H.

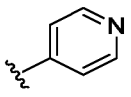
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

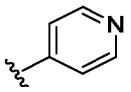
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

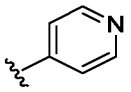
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

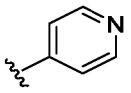
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is H.

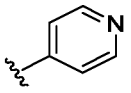
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

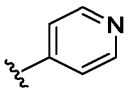
In some embodiments, W is N, Y is CH, R^1 is isopropyl, and R^3 is H. R^2 is isopropyl, Ring A is , and R^3 is H.

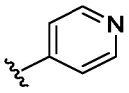
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

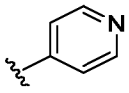
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is H.

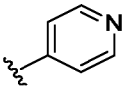
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Ring A is , and R^3 is H.

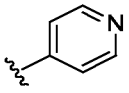
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Ring A is , and R^3 is H.

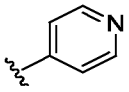
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Ring A is , and R^3 is H.

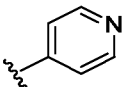
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Ring A is , and R^3 is H.

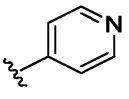
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Ring A is , and R^3 is H.

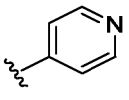
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Ring A is , and R^3 is -CH_3.

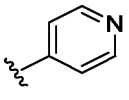
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Ring A is , and R^3 is -CH_3.

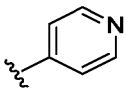
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Ring A is , and R^3 is -CH_3.

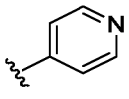
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

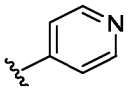
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

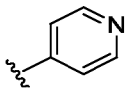
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

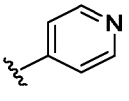
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

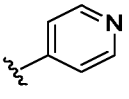
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

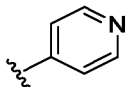
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is -CH_3.

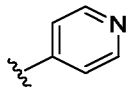
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is -CH_3.

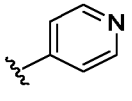
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is -CH_3.

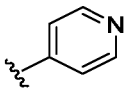
In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , and R^3 is H.

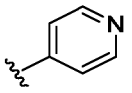
In some embodiments, W is N, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , and R^3 is H.

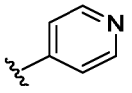
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is H.

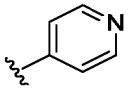
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is $-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$.

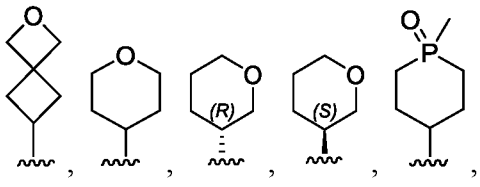
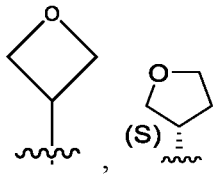
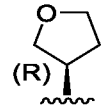
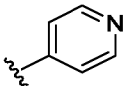
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , and R^3 is H.

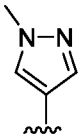
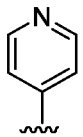
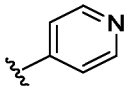
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

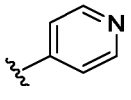
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

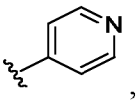
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

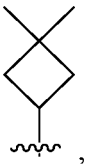
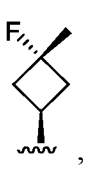
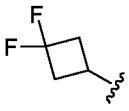
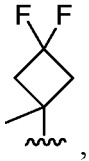
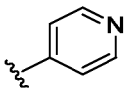
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , and R^3 is H.

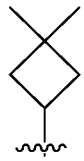
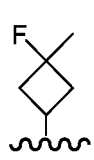
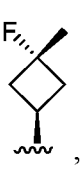
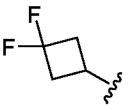
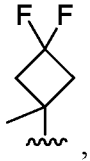
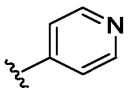
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Ring A is , and R^3 is H.

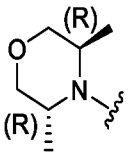
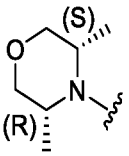
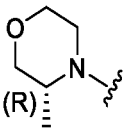
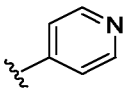
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , and R^3 is H.

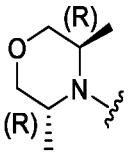
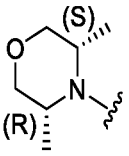
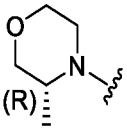
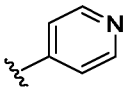
In some embodiments, W is N, Y is N, R^1 is , , , , , , or , R^2 is isopropyl, Ring A is , and R^3 is H.

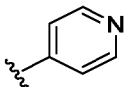
In some embodiments, W is CH, Y is N, R^1 is , , , , , , or , R^2 is isopropyl, Ring A is , and R^3 is H.

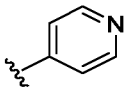
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

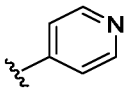
, , , Ring A is , and R^3 is H.

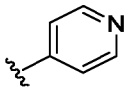
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

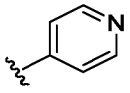
, , , Ring A is , and R^3 is H.

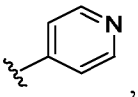
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

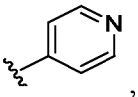
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

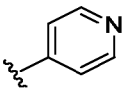
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

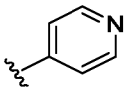
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

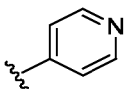
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

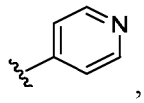
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

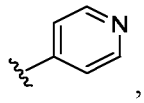
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

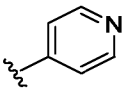
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

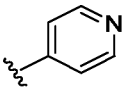
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

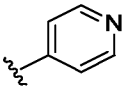
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

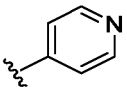
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

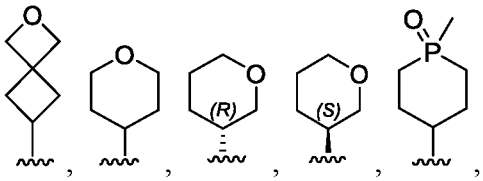
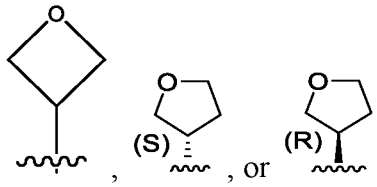
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

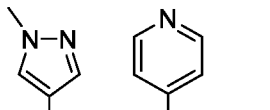
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

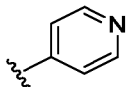
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

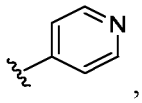
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

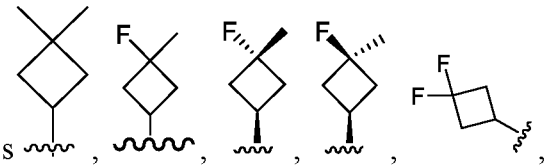
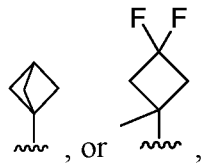
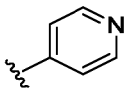
In some embodiments, W is CH, Y is N, R^1 is , , and R^3 is H.

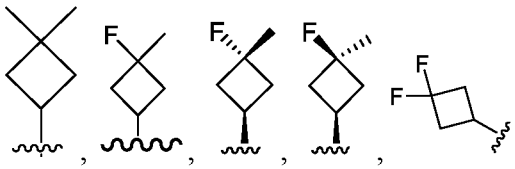
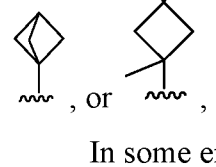
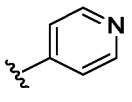
In some embodiments, W is CH, Y is N, R^1 is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , and R^3 is H.

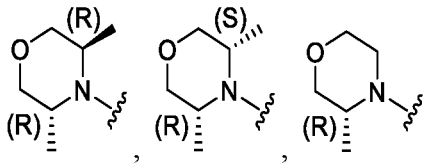
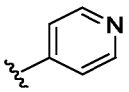
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

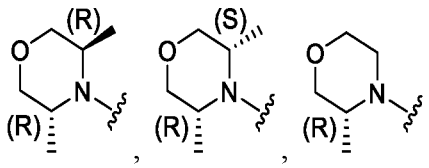
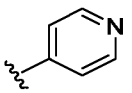
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

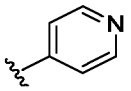
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

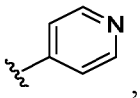
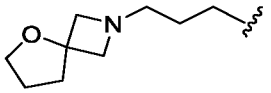
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

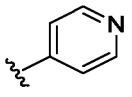
, Z is O, Ring A is , and R^3 is H.

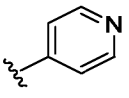
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

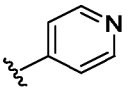
, Z is O, Ring A is , and R^3 is H.

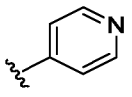
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is , and R^3 is H.

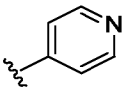
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is  , and R^3 is  .

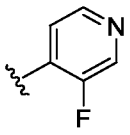
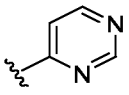
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is  , and R^3 is H.

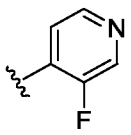
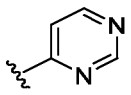
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, Ring A is  , and R^3 is H.

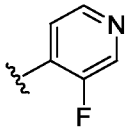
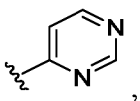
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, Ring A is  , and R^3 is H.

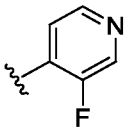
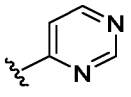
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, Ring A is  , and R^3 is H.

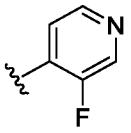
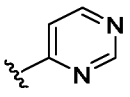
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, Ring A is  , and R^3 is H.

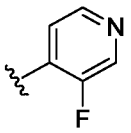
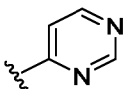
In some embodiments, W is CH, Y is N, Ring A is  , or  , and R^3 is H.

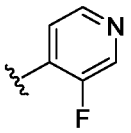
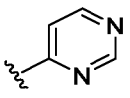
In some embodiments, W is CH, Y is N, R^1 is ethyl, Ring A is  , or  , and R^3 is H.

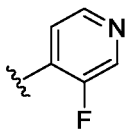
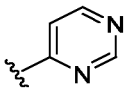
In some embodiments, W is CH, Y is N, R^1 is isopropyl, Ring A is  , or  , and R^3 is H.

In some embodiments, W is CH, Y is N, R^2 is isopropyl, Ring A is , or , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , or , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , or , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , or , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , or , and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, X^3 is H, and R^3 is -CH_3.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, X^3 is H, and R^3 is -CH_3.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, X^3 is H, and R^3 is -CH_3.

In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, X^3 is H, and R^3 is H.

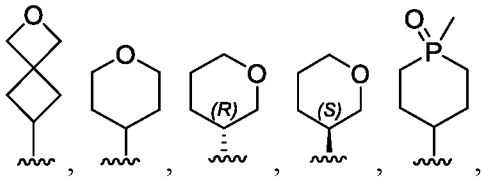
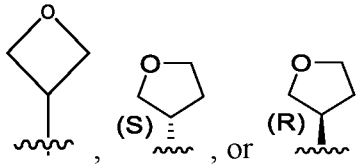
In some embodiments, W is CH, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, X^3 is H, and R^3 is H.

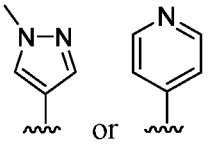
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, X^3 is H, and R^3 is H.

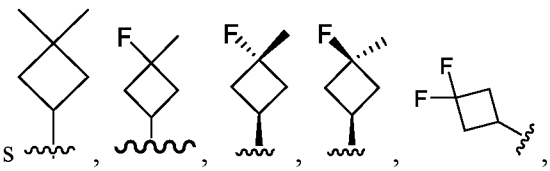
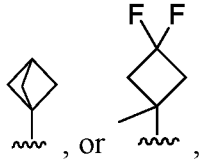
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, X^3 is H, and R^3 is H.

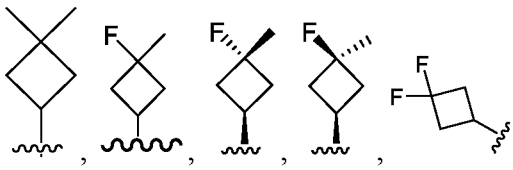
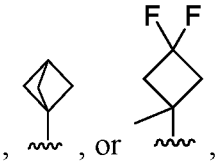
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

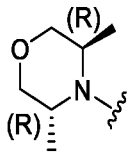
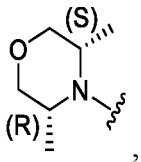
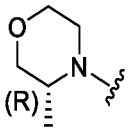
In some embodiments, W is N, Y is CH, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl and R^2 is isopropyl, X^3 is H, and R^3 is H.

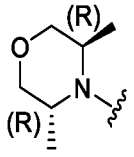
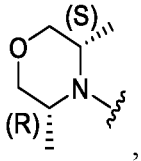
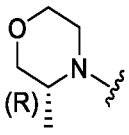
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:




, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:




, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is $-CH_3$.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is $-CH_3$.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is $-CH_3$.

In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

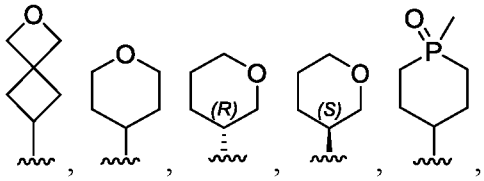
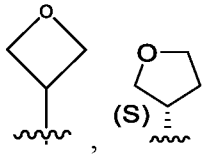
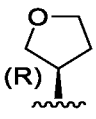
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

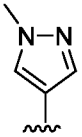
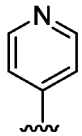
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

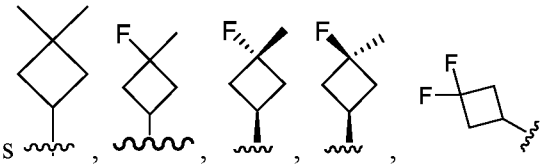
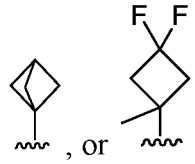
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

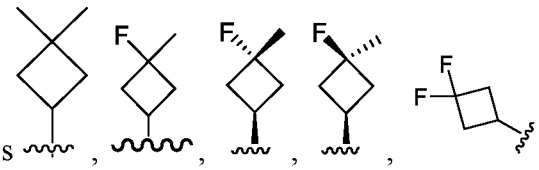
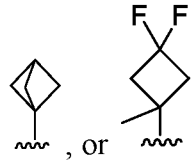
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

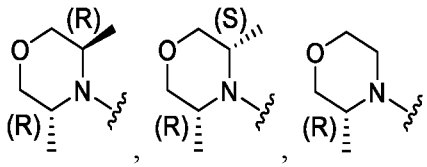
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

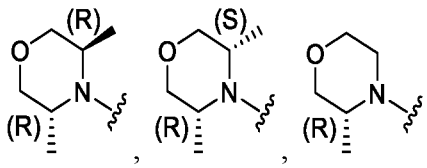
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

, Z is O, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, Z is NH, X^3 is H, and R^3 is H.

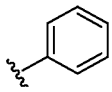
In some embodiments, W is CH, Y is N, R^1 is ethyl, Z is NH, X^3 is H, and R^3 is H.

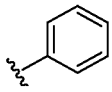
In some embodiments, W is CH, Y is N, R^1 is isopropyl, Z is NH, X^3 is H, and R^3 is H.

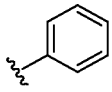
In some embodiments, W is CH, Y is N, R^2 is isopropyl, Z is NH, X^3 is H, and R^3 is H.

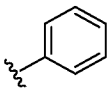
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, X^3 is H, and R^3 is H.

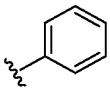
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, X^3 is H, and R^3 is H.

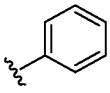
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

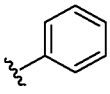
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

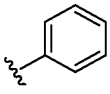
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

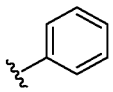
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

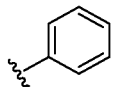
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

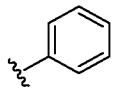
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

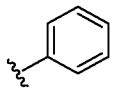
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

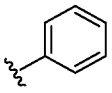
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

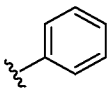
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

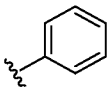
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

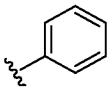
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

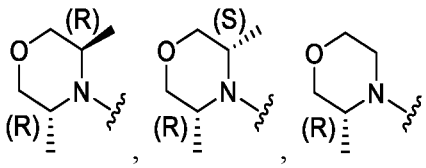
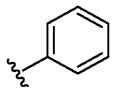
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

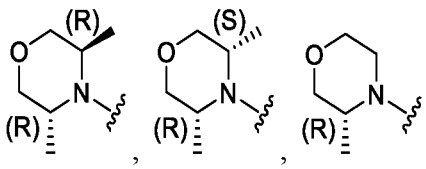
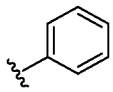
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

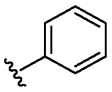
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

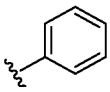
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

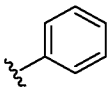
, Ring A is , X^3 is H, and R^3 is H.

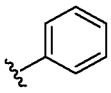
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

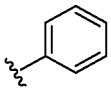
, Ring A is , X^3 is H, and R^3 is H.

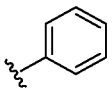
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

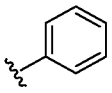
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

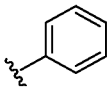
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

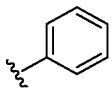
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

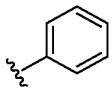
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

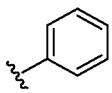
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

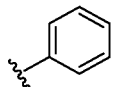
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

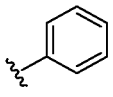
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

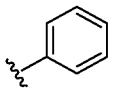
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

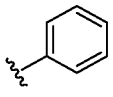
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

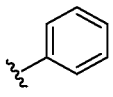
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

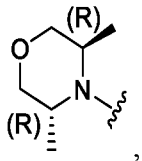
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

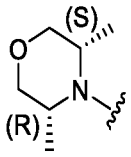
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

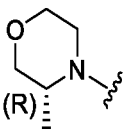
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

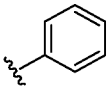
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

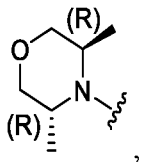


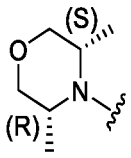
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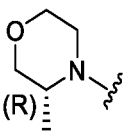
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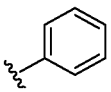
, Z is O, Ring A is , X^3 is H, and R^3 is H.

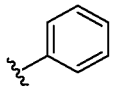
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

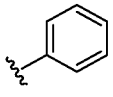


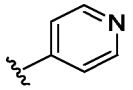
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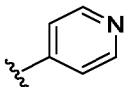
, Z is O, Ring A is , X^3 is H, and R^3 is H.

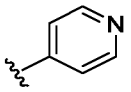
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, Ring A is , X^3 is H, and R^3 is H.

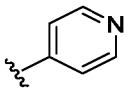
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, Ring A is , X^3 is H, and R^3 is H.

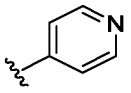
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is 

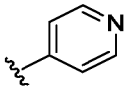
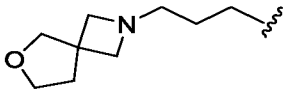
, X^3 is H, and R^3 is H.

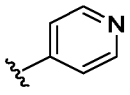
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

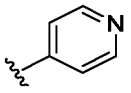
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

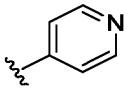
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

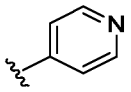
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

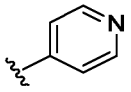
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is .

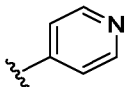
In some embodiments, W is N, Y is CH, R^1 is isopropyl, X^3 is H, and R^3 is H. R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

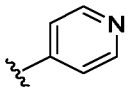
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

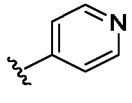
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

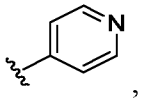
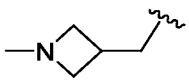
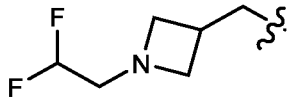
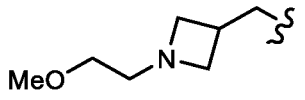
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

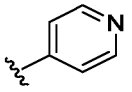
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

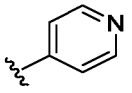
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

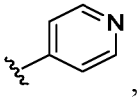
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is -CH_2-CH_2-$N(CH_3)_2$, -CH_2-CH_2-CH_2-$N(CH_3)_2$, -CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$, or -CH_2-CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$.

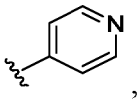
In some embodiments, W is CH, Y is CH, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

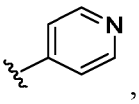
In some embodiments, W is N, Y is N, R^1 is -CH_2-CF_3, or -CH_2-CHF_2, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is , , or .

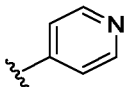
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

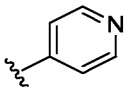
In some embodiments, W is CH, Y is N, R^1 is CH_2-CN, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

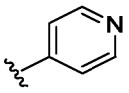
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

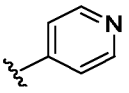
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

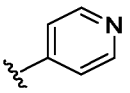
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

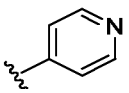
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is $-CH_3$.

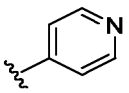
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is $-CH_3$.

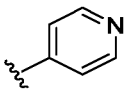
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is $-CH_3$.

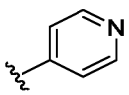
In some embodiments, W is N, Y is N, R^1 is $-CH_2$-phenyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

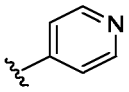
In some embodiments, W is CH, Y is N, R^1 is CH_2-CN, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

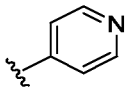
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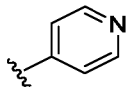
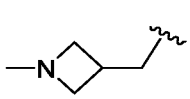
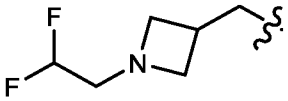
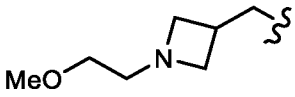
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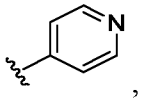
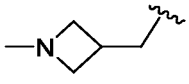
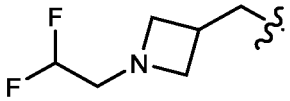
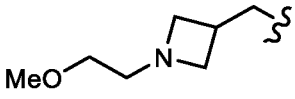
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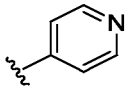
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is $-CH_3$.

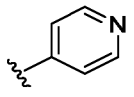
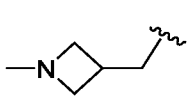
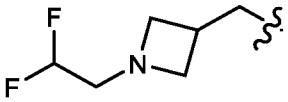
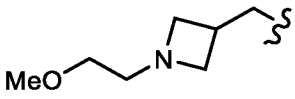
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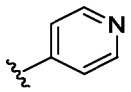
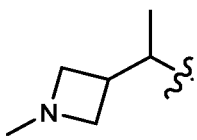
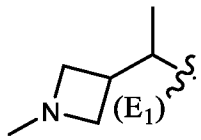
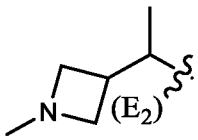
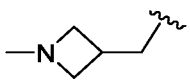
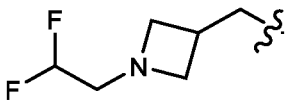
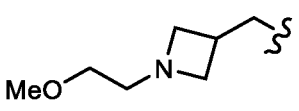
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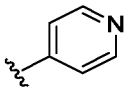
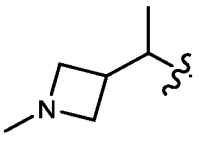
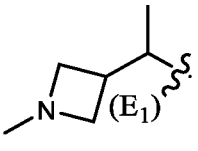
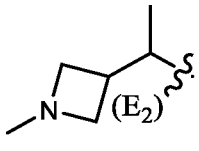
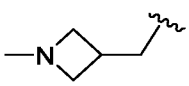
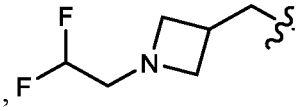
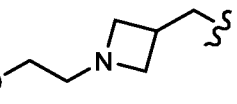
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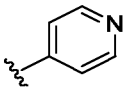
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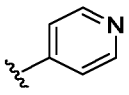
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is $-CH_2-CH_2-CH_2-NH_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, or $-CH_2-CH_2-CH_2-N(CH_2-CH_3)_2$.

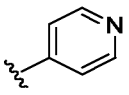
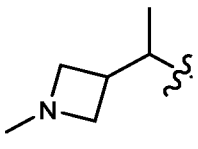
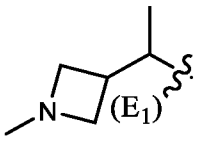
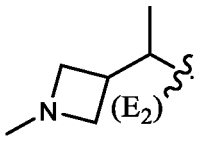
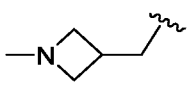
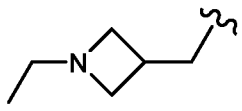
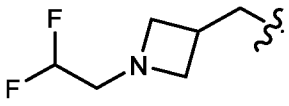
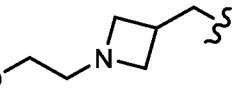
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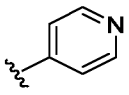
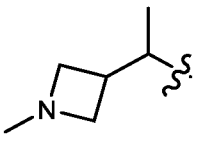
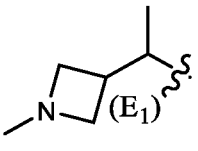
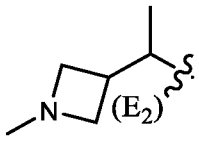
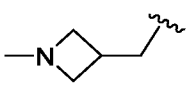
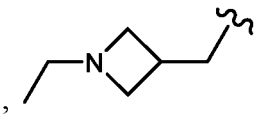
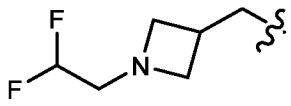
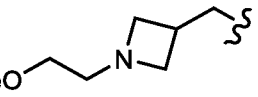
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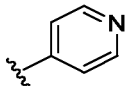
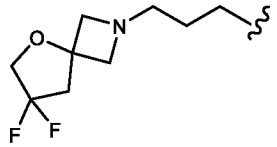
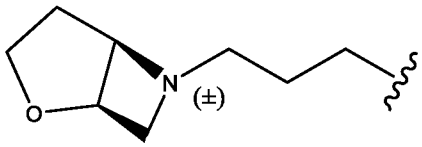
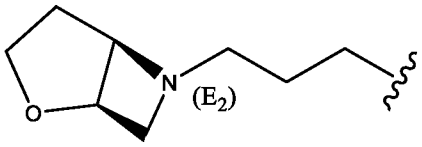
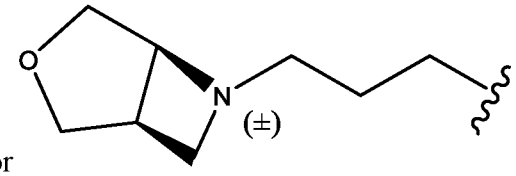
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is , , , , , or .

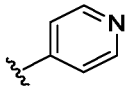
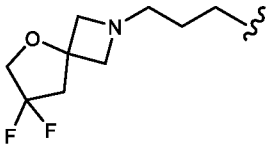
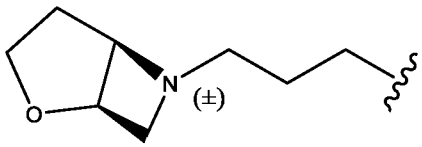
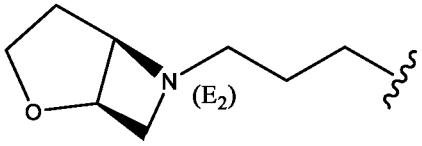
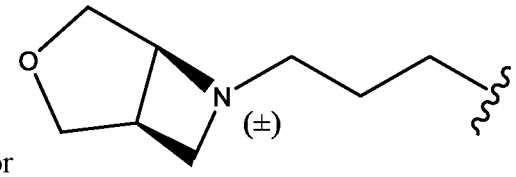
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is -CH_2-CH_2-CH_2-S(=O)$_2$Me.

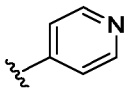
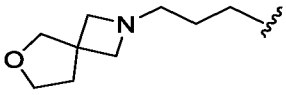
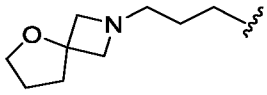
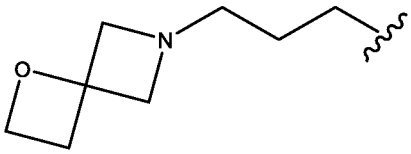
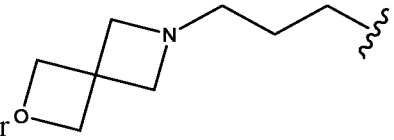
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is -CH_2-CH_2-CH_2-S(=O)$_2$Me.

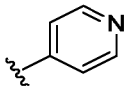
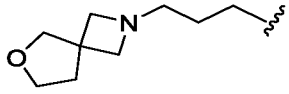
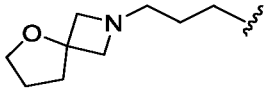
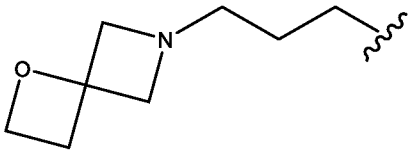
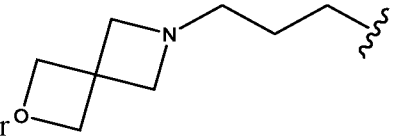
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is , , , , , , or .

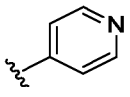
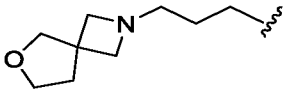
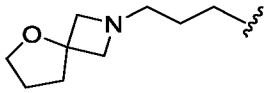
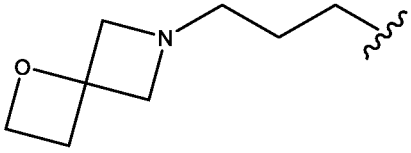
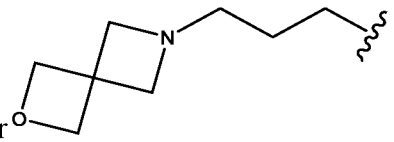
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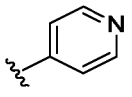
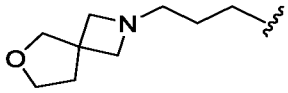
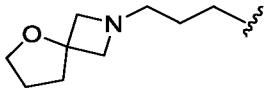
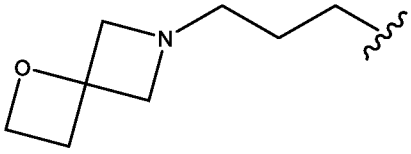
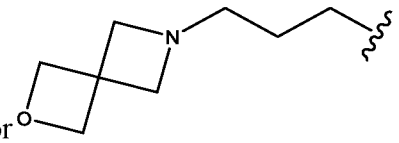
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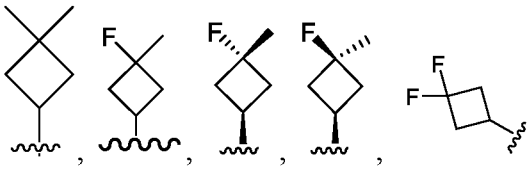
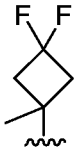
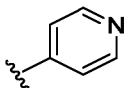
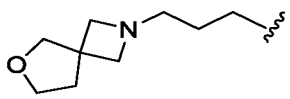
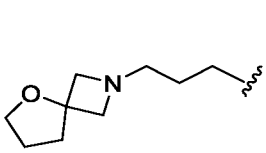
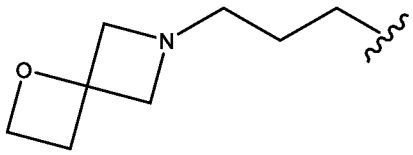
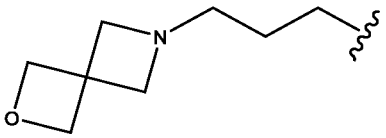
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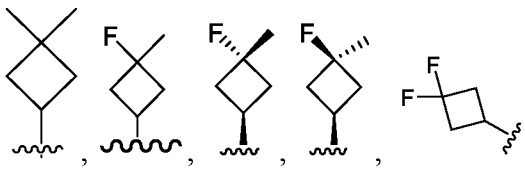
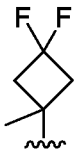
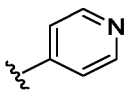
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is , , , or .

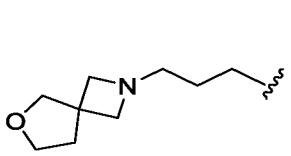
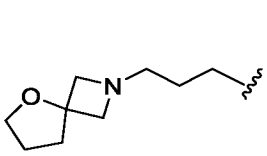
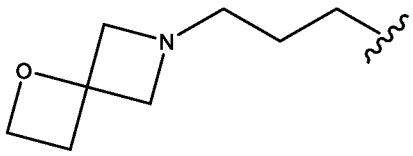
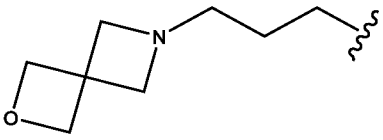
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is , , , or .

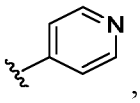
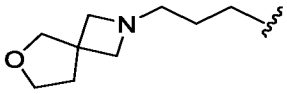
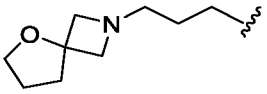
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is , , , , or .

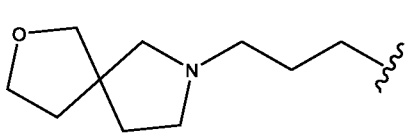
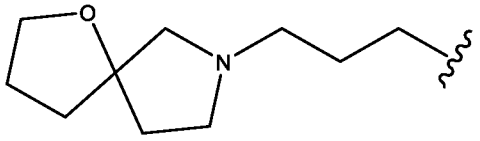
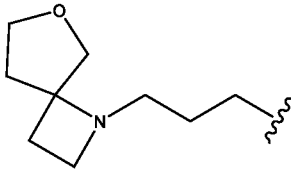
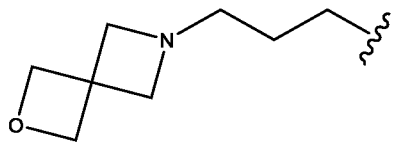
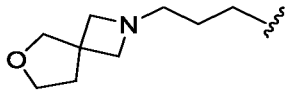
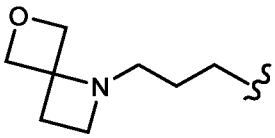
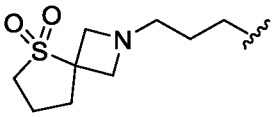
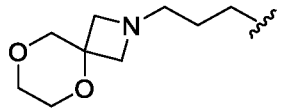
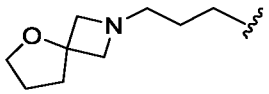
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is , , , , or .

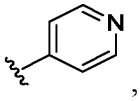
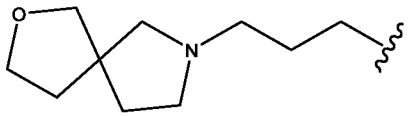
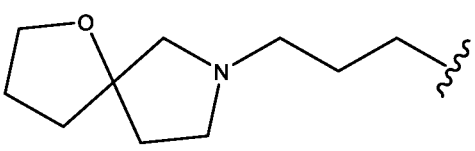
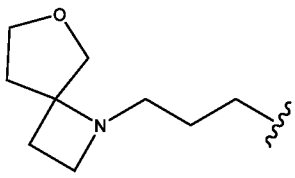
In some embodiments, W is N, Y is N, R^1 is , , , or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is , , , or .

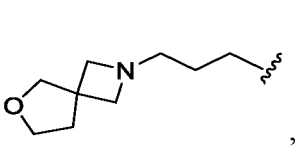
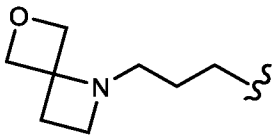
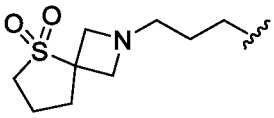
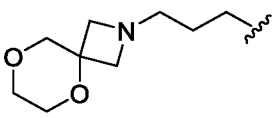
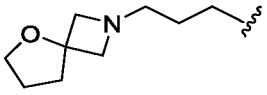
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is

, , , or .

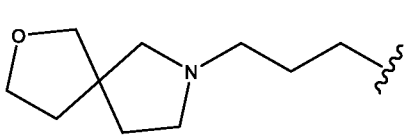
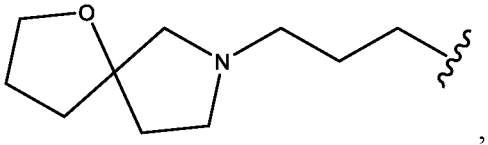
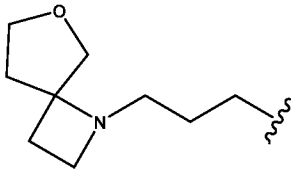
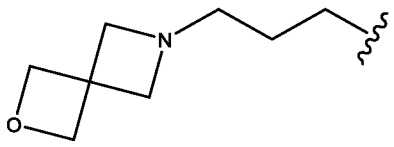
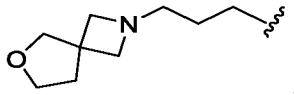
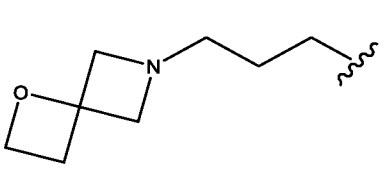
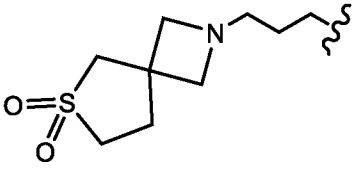
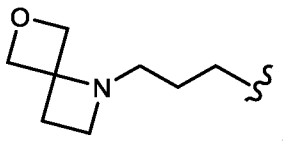
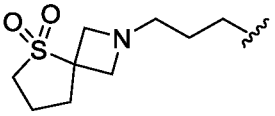
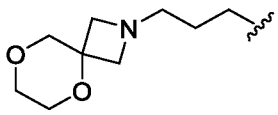
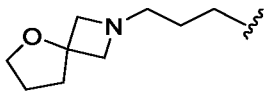
In some embodiments, W is N, Y is N, R^1 is methyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is  or .

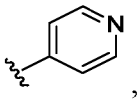
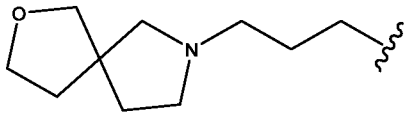
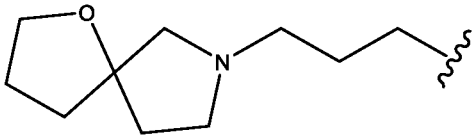
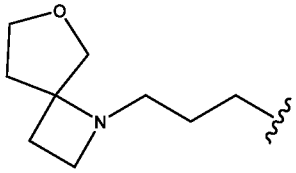
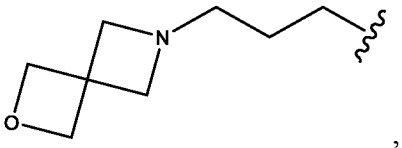
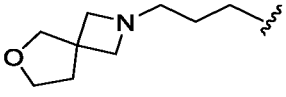
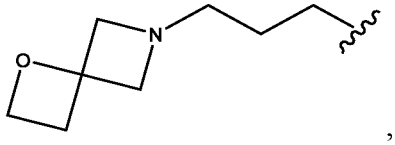
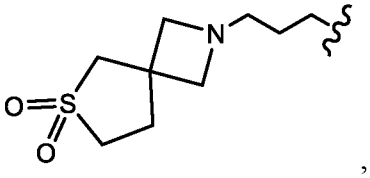
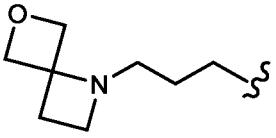
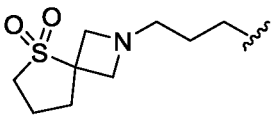
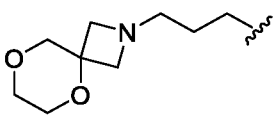
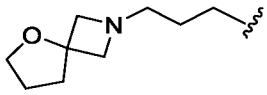
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is , , , , , , , , or .

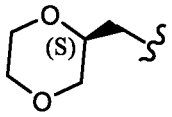
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is , , , .

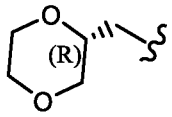
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or .

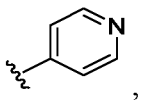
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is , , , , , , , , , , .

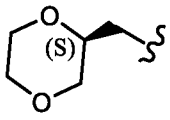
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is , , , , , , , , , , .

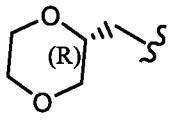
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is 

, or 

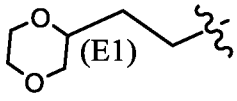
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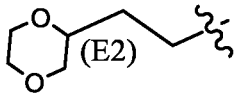
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 

, X^3 is H, and R^3 is 

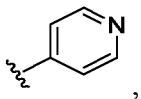
, or 

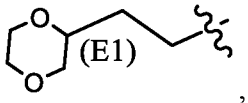
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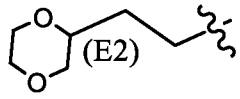
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is 

, or 

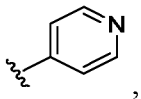
.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 

, X^3 is H, and R^3 is 

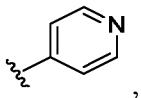
, or 

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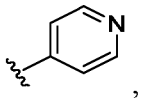
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 

, and X^3 is $-CH_2-O-CH_2-CHF_2$.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is $-CH_2-O-CH_2-CHF_2$, and R^3 is H.

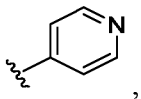
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 

, X^3 is $-CH_2-O-CH_2-CHF_2$, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 

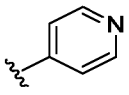
, and X^3 is $-CH_2-CH_2-S(O)_2-CH_3$ or $-CH_2-CH_2-CH_2-S(O)_2-CH_3$.

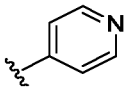
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is $-CH_2-CH_2-S(O)_2-CH_3$ or $-CH_2-CH_2-CH_2-S(O)_2-CH_3$, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 

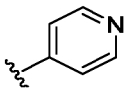
, X^3 is $-CH_2-CH_2-S(O)_2-CH_3$ or $-CH_2-CH_2-CH_2-S(O)_2-CH_3$, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-$S(O)_2$-CH_3 or -CH_2-CH_2-CH_2-$S(O)_2$-CH_3, and R^3 is methyl.

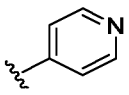
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-$S(O)_2$-CH_3 or -CH_2-CH_2-CH_2-$S(O)_2$-CH_3, and R^3 is methyl.

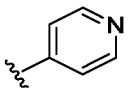
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is -CH_2-CH_2-CH_2-O-CHF_2.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is X^3 is -CH_2-CH_2-CH_2-O-CHF_2, and R^3 is H.

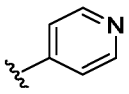
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-CH_2-O-CHF_2, and R^3 is H.

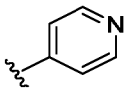
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-CH_2-O-CHF_2, and R^3 is methyl.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-CH_2-O-CHF_2, and R^3 is methyl.

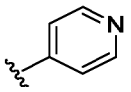
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is -CH_2-O-CH_2-CH_2-$N(CH_3)_2$.

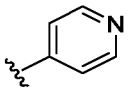
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-O-CH_2-CH_2-$N(CH_3)_2$, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-O-CH_2-CH_2-$N(CH_3)_2$, and R^3 is H.

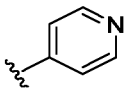
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is -CH_2-CH_2-OH.

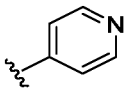
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-OH, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-OH, and R^3 is H.

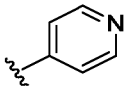
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is -CH_2-CH_2-CH_2-$N(CH_3)_2$.

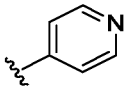
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-CH_2-$N(CH_3)_2$, and R^3 is methyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-CH_2-$N(CH_3)_2$, and R^3 is methyl.

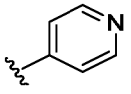
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is -CH_2-CH_2-NH-C(O)-CH_3.

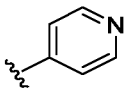
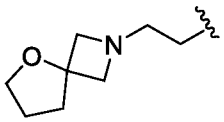
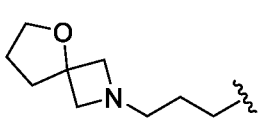
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-NH-C(O)-CH_3, and R^3 is H.

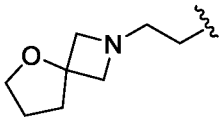
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-NH-C(O)-CH_3, and R^3 is H.

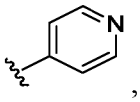
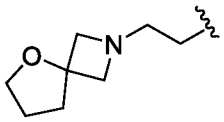
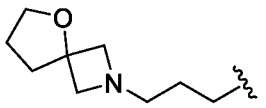
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is -CH_2-CH_2-NH-S(O)$_2$-CH_3.

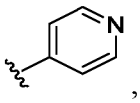
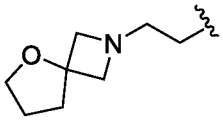
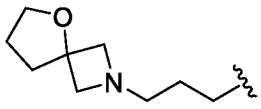
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-NH-S(O)$_2$-CH_3, and R^3 is H.

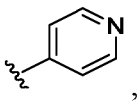
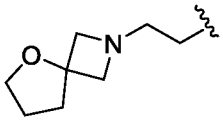
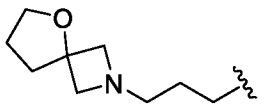
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-NH-S(O)$_2$-CH_3, and R^3 is H.

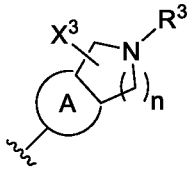
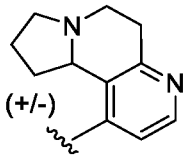
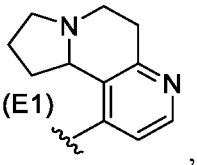
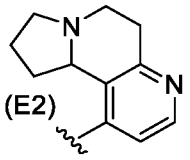
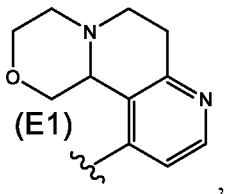
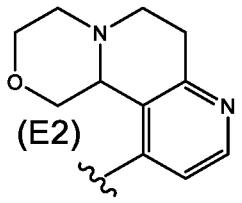
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , and X^3 is  or .

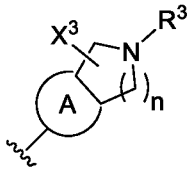
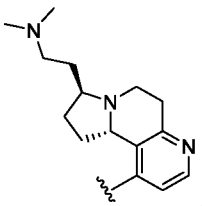
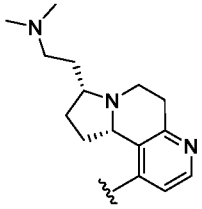
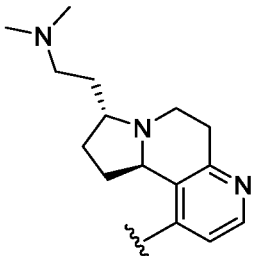
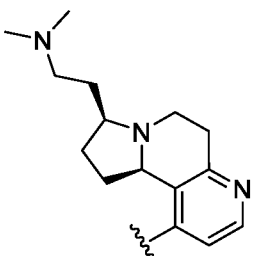
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is , and R^3 is H.

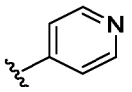
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and X^3 is  or .

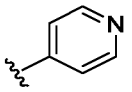
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is  or , and R^3 is H.

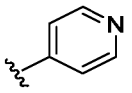
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is  or , and R^3 is H.

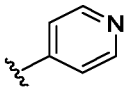
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O,  is , , , , or .

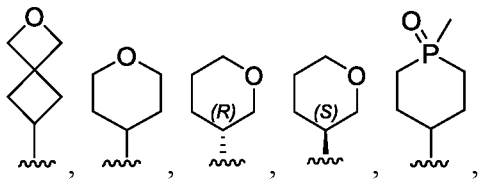
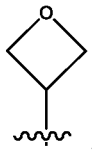
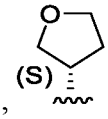
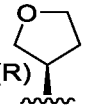
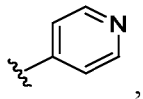
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O,  is , , , or .

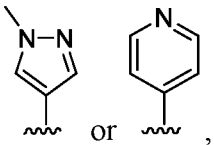
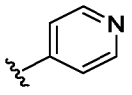
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

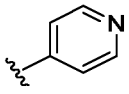
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

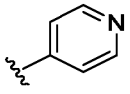
In some embodiments, W is CH, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

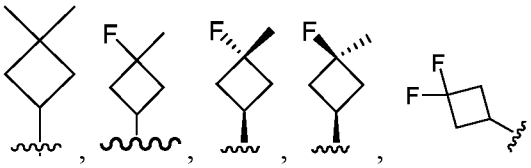
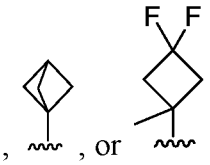
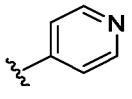
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

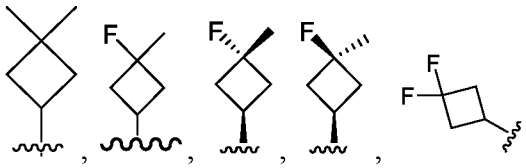
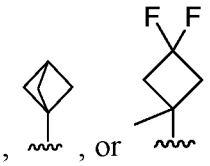
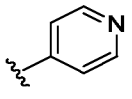
In some embodiments, W is CH, Y is N, R^1 is , , , or , R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

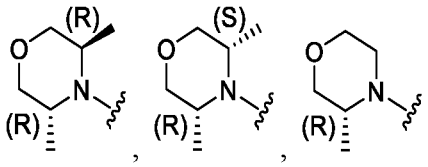
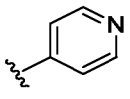
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

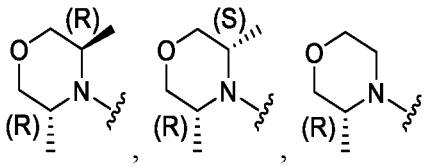
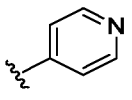
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

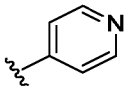
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is H.

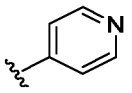
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

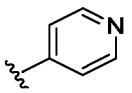
, Ring A is , X^3 is H, and R^3 is H.

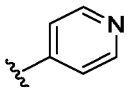
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

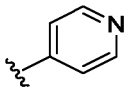
, Ring A is , X^3 is H, and R^3 is H.

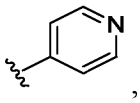
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

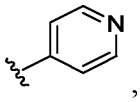
In some embodiments, W is N, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

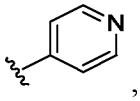
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

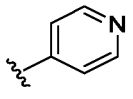
In some embodiments, W is CH, Y is CH, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

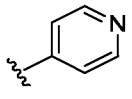
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

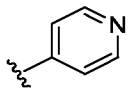
In some embodiments, W is N, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

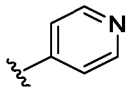
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

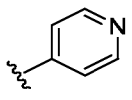
In some embodiments, W is CH, Y is CH, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

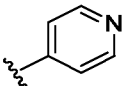
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

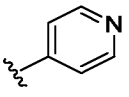
In some embodiments, W is N, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

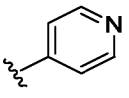
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

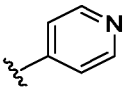
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is methyl, ethyl, or isopropyl, and R^3 is H.

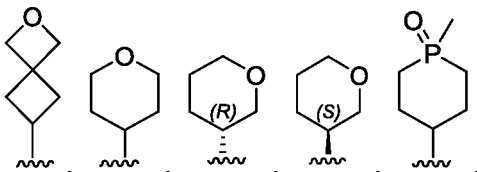
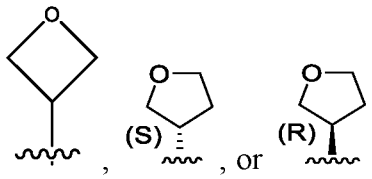
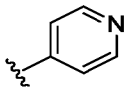
In some embodiments, W is CH, Y is CH, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

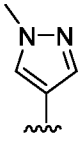
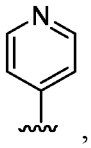
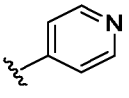
In some embodiments, W is N, Y is N, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

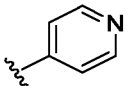
In some embodiments, W is N, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

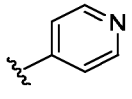
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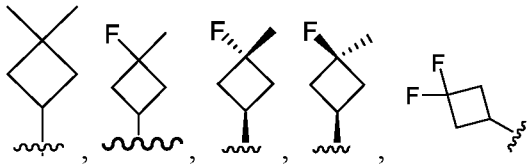
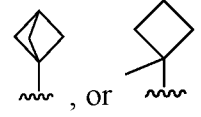
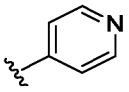
In some embodiments, W is CH, Y is CH, R^1 is -CH=CHF, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

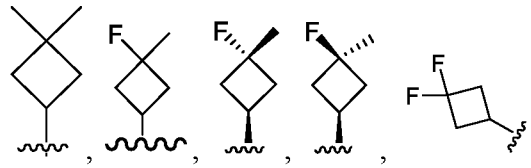
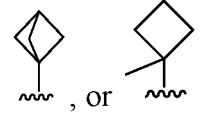
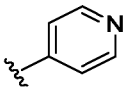
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is  or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

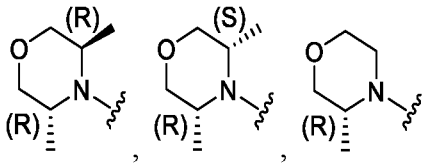
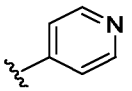
In some embodiments, W is N, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclopropyl or cyclobutyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

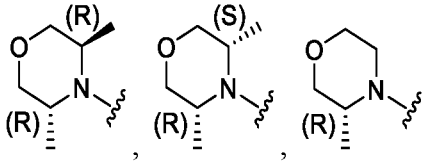
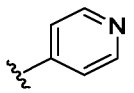
In some embodiments, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

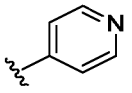
In some embodiments, W is CH, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

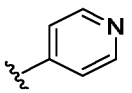
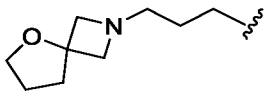
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

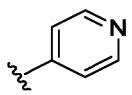
, Z is O, Ring A is , X^3 is H, and R^3 is H.

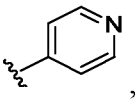
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

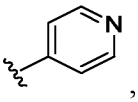
, Z is O, Ring A is , X^3 is H, and R^3 is H.

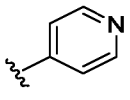
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is , X^3 is H, and R^3 is H.

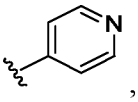
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is , X^3 is H, and R^3 is .

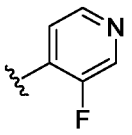
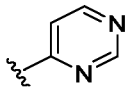
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is CH_2, Ring A is , X^3 is H, and R^3 is H.

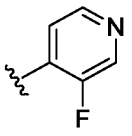
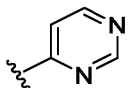
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, Ring A is , X^3 is H, and R^3 is H.

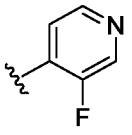
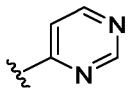
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is CH_2, Ring A is , X^3 is H, and R^3 is H.

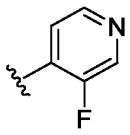
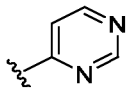
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is NH, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is NH, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is  or , X^3 is H, and R^3 is H.

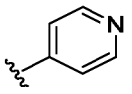
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is  or , X^3 is H, and R^3 is H.

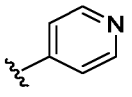
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is  or , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is  or , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, X^3 is -CH_2-CH_2-CH_2(OH), and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is -CH_2-CH_2-CH_2(OH), and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is -CH_2-CH_2-CH_2(OH), and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is -CH_2-CH_2-CH_2(OH), and R^3 is H.

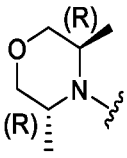
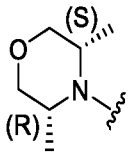
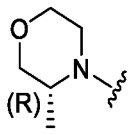
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, and R^3 is methyl, ethyl, or isopropyl.

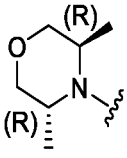
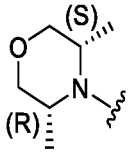
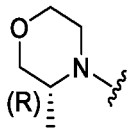
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, , and , and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

, , and , and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, Z is O, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, Z is O, and R^3 is H.

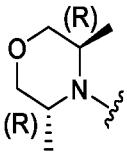
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, and R^3 is H.

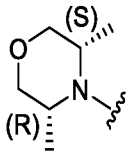
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, and R^3 is -CH_3.

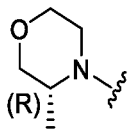
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, and R^3 is -CH_3.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Z is O, and R^3 is -CH_3.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

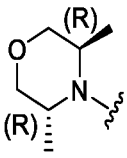


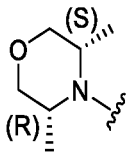
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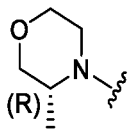
, and 

, Z is O, and R^3 is methyl, ethyl, or isopropyl.

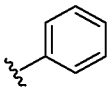
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

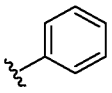


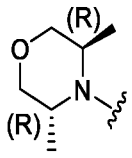
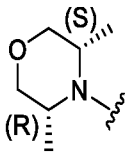
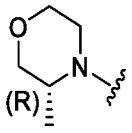
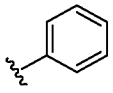
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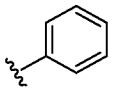
, and 

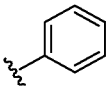
, Z is O, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , and R^3 is methyl, ethyl, or isopropyl.

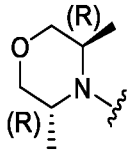
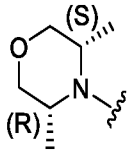
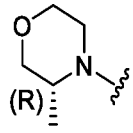
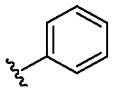
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , and R^3 is methyl, ethyl, or isopropyl. In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

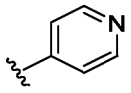


, and 
, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

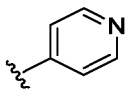
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

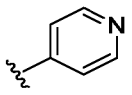
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

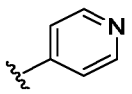
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

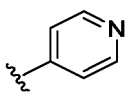


, and 
, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

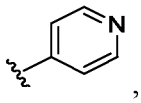
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

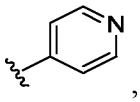
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

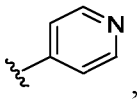
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

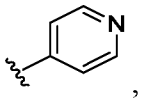
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

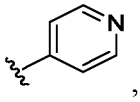
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Ring A is 
, and R^3 is H.

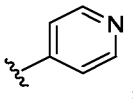
In some embodiments, W is CH, Y is N, R^1 is -CH_2-CN, R^2 is isopropyl, Z is O, Ring A is , and R^3 is H.

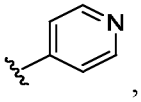
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, Z is O, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, Z is O, Ring A is , and R^3 is H.

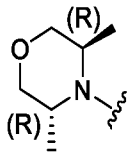
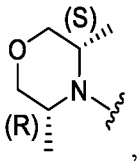
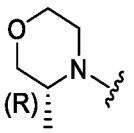
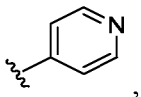
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Ring A is , and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Ring A is , and R^3 is -CH_3.

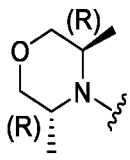
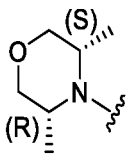
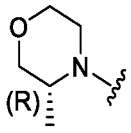
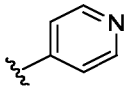
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Ring A is , and R^3 is -CH_3.

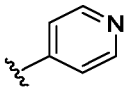
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Ring A is , and R^3 is -CH_3.

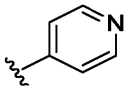
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

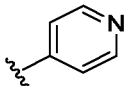
, , and , Ring A is , and R^3 is methyl, ethyl, or isopropyl.

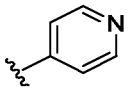
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

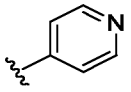


, and 
, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

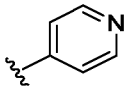
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

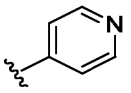
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

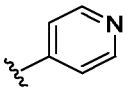
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

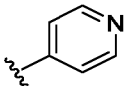
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is methyl, ethyl, or isopropyl.

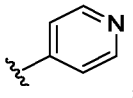
In some embodiments, W is N, Y is N, R^1 is -CH_2-phenyl, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is H.

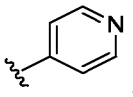
In some embodiments, W is CH, Y is N, R^1 is CH_2-CN, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is H.

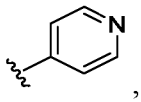
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is H.

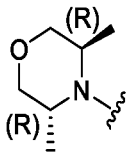
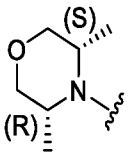
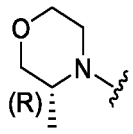
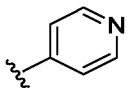
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, Ring A is 
, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is $-CH_3$.

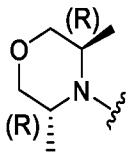
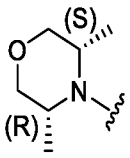
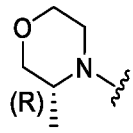
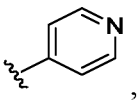
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , and R^3 is $-CH_3$.

In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group, Z is O, R^2 is isopropyl, Ring A is , and R^3 is $-CH_3$.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, , and , Z is O, Ring A is , and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

, , and , Z is O, Ring A is , and R^3 is methyl, ethyl, or isopropyl.

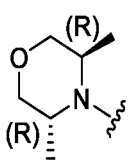
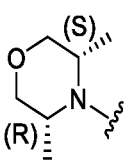
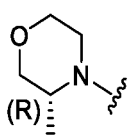
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

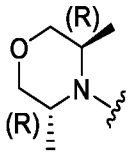
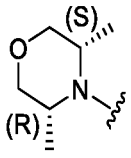
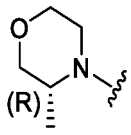
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

, , and , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:



, and  X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

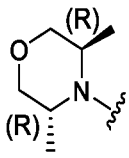
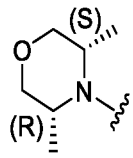
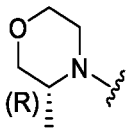
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

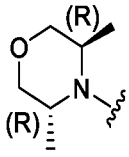
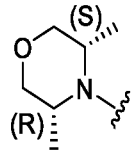
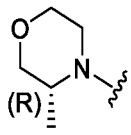
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

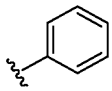
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

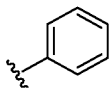
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

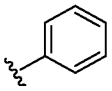


, and  , Z is O, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

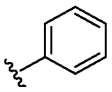
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

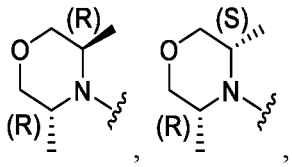
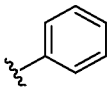


, and  , Z is O, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

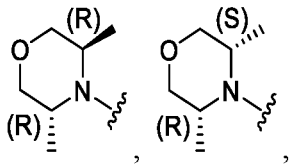
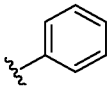
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

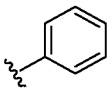
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

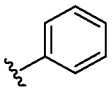
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

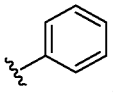
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

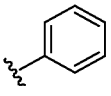
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from: , Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

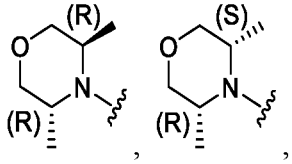
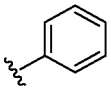
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from: , Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

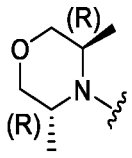
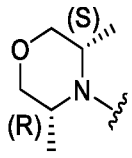
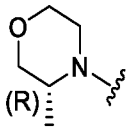
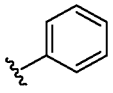
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

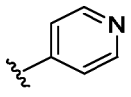
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

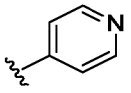
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

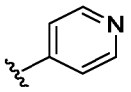
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from: , Z is O, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

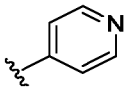
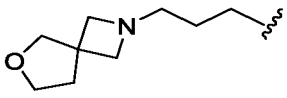
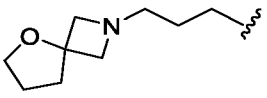
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

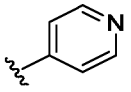
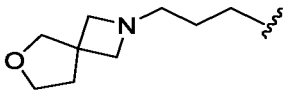
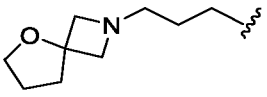


, and 
, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

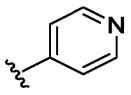
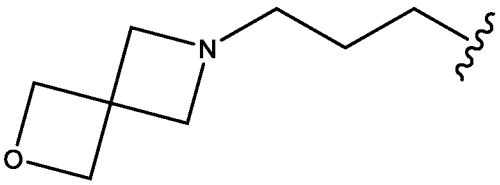
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

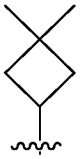
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

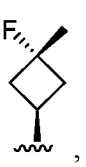
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

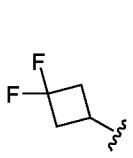
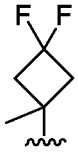
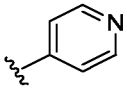
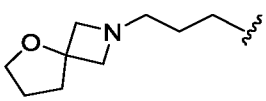
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is 
, X^3 is H, and R^3 is 
or 
.

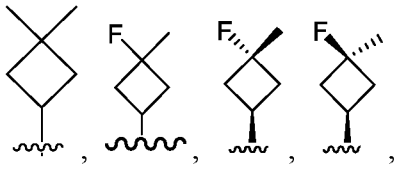
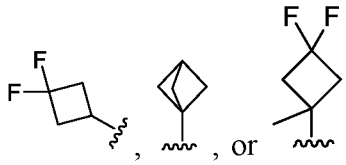
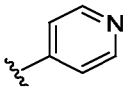
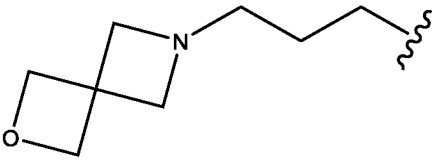
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is 
, X^3 is H, and R^3 is 
or 
.

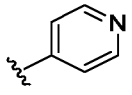
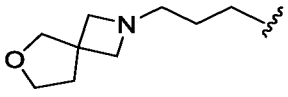
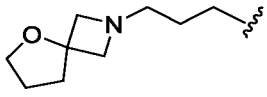
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Ring A is 
, Z is O, X^3 is H, and R^3 is 
.

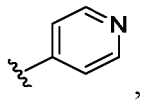
In some embodiments, W is N, Y is N, R^1 is 



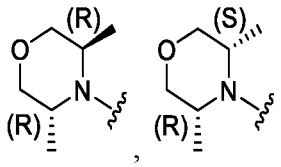
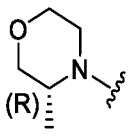
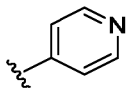

, 
, or 
, R^2 is isopropyl, Z is O, Ring A is 
, Z is O, X^3 is H, and R^3 is 
.

In some embodiments, Z is O, W is N, Y is N, R^1 is , , or , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

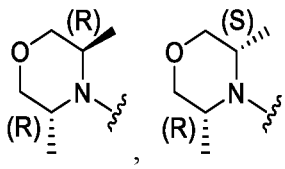
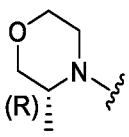
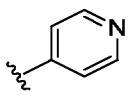
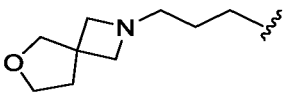
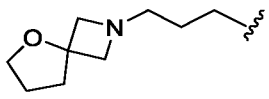
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, or $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is  or .

In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

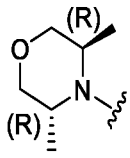
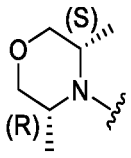
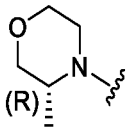
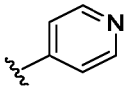
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

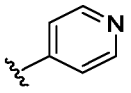
, , and , Ring A is , X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

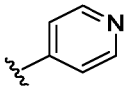
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

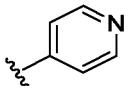
, , and , Ring A is , X^3 is H, and R^3 is  or .

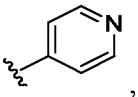
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:



, and 
, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

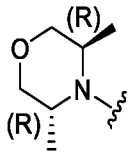
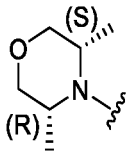
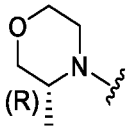
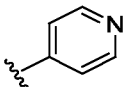
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

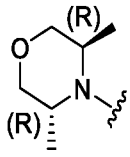
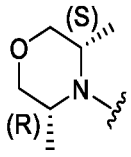
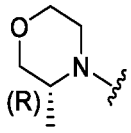
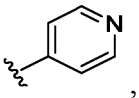
In some embodiments, W is N, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

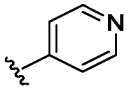
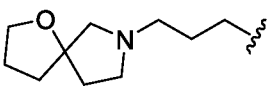
In some embodiments, W is CH, Y is N, R^1 is isopropyl, R^2 is isopropyl, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

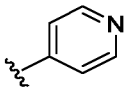
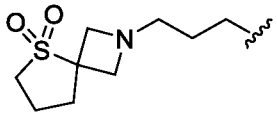
In some embodiments, W is N, Y is N, R^1 and R^2 form a group selected from:

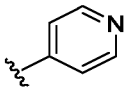
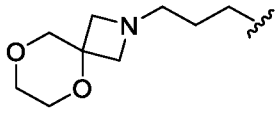


, and 
, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

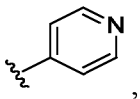
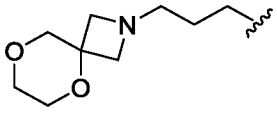
In some embodiments, W is CH, Y is N, R^1 and R^2 form a group selected from:

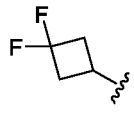
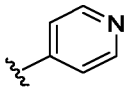
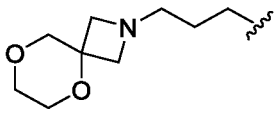


, and 
, Z is O, Ring A is 
, X^3 is H, and R^3 is methyl, ethyl, or isopropyl.

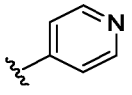
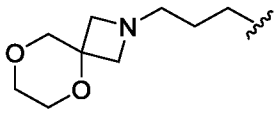
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is 
, X^3 is H, and R^3 is 
.

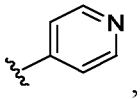
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

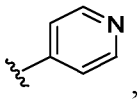
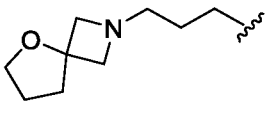
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

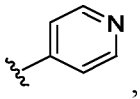
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CHF_2$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

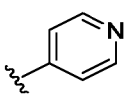
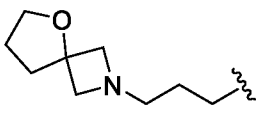
In some embodiments, W is N, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

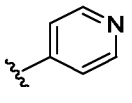
In some embodiments, W is N, Y is N, R^1 is $-CH_2-CF_3$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

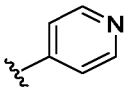
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CN$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

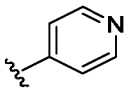
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CN$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is .

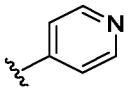
In some embodiments, W is N, Y is N, R^1 is $-CH_2$-phenyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

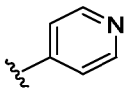
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is , and R^3 is H.

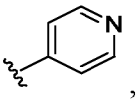
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

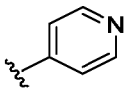
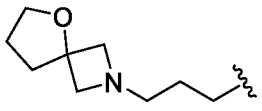
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one methoxy group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

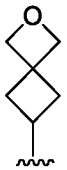
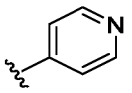
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

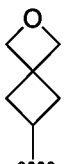
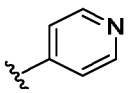
In some embodiments, W is N, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is $-CD_3$.

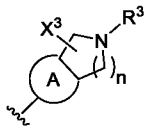
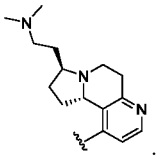
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one OH and one methyl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

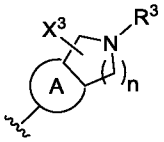
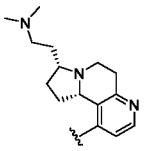
In some embodiments, W is CH, Y is N, R^1 is $-CH_2-CN$, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

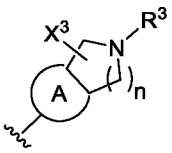
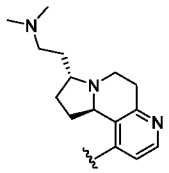
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O, Ring A is , X^3 is , and R^3 is methyl.

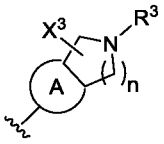
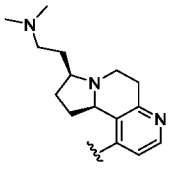
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

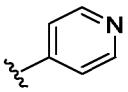
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

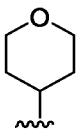
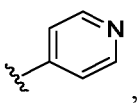
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O,  is .

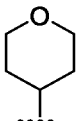
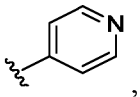
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O,  is .

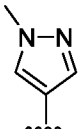
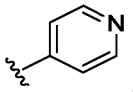
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O,  is .

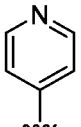
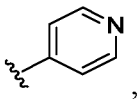
In some embodiments, W is CH, Y is N, R^1 is ethyl, R^2 is isopropyl, Z is O,  is .

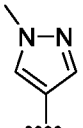
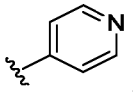
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one CN and one methyl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

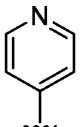
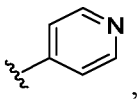
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

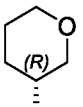
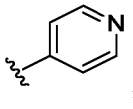
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

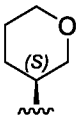
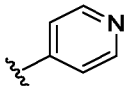
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

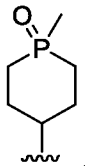
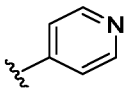
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

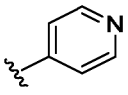
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

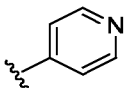
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

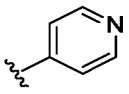
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

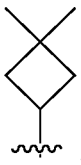
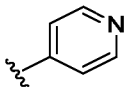
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

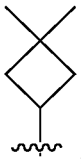
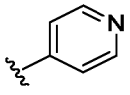
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

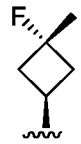
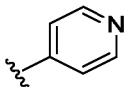
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-pyrazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

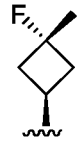
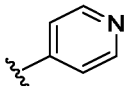
In some embodiments, W is CH, Y is N, R^1 is cyclobutyl substituted by one 1H-imidazol-1-yl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

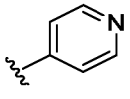
In some embodiments, W is CH, Y is N, R^1 is one 1H-imidazol-1-yl group and one methyl group, R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

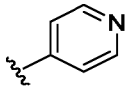
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl.

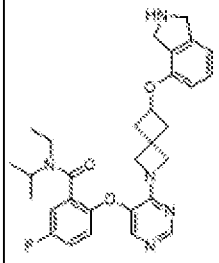
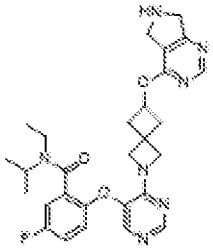
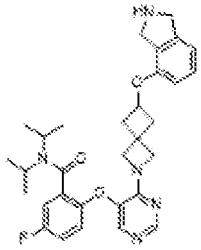
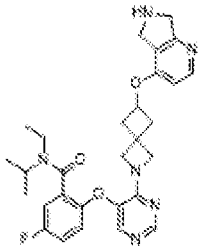
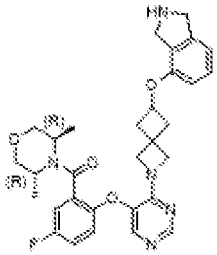
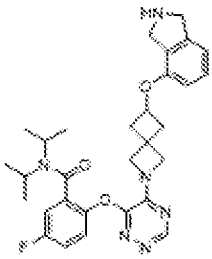
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is H.

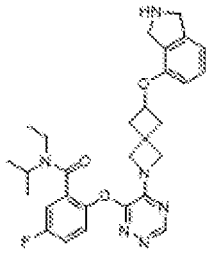
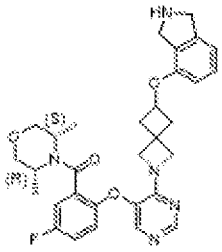
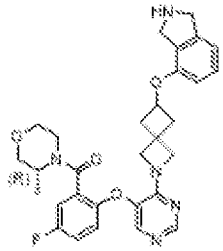
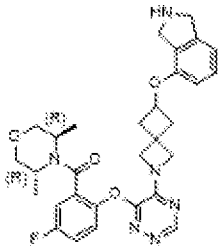
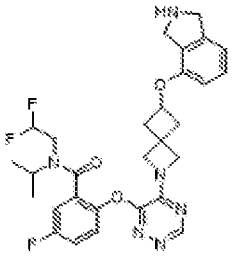
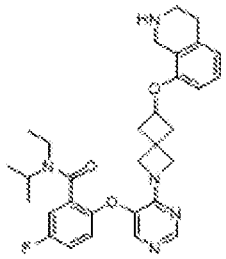
In some embodiments, W is CH, Y is N, R^1 is , R^2 is isopropyl, Z is O, Ring A is , X^3 is H, and R^3 is methyl. In some embodiments, the compound is of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, or III combined with any of the embodiments described herein.

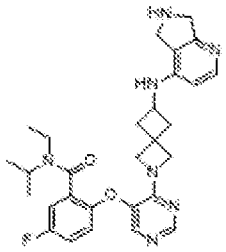
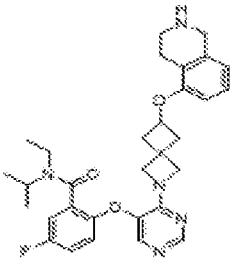
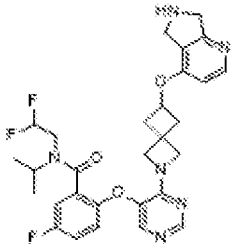
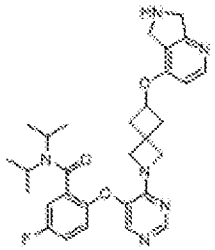
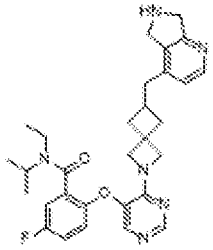
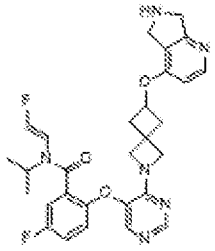
Any of the groups described above for any variable can be combined with any of the other groups described above, where applicable, for any of the Formulae described herein.

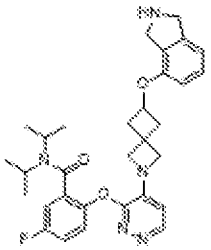
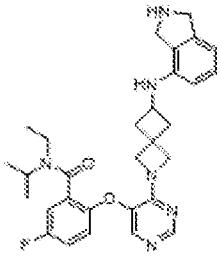
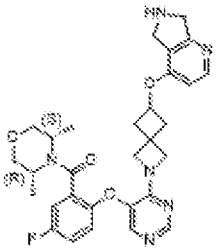
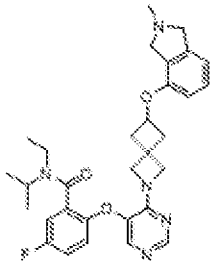
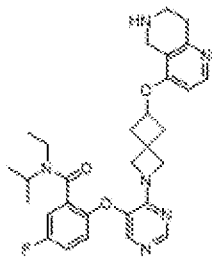
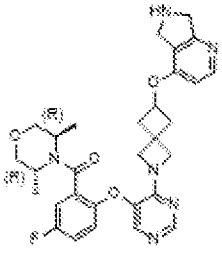
Representative compounds of the present disclosure are shown in the table below.

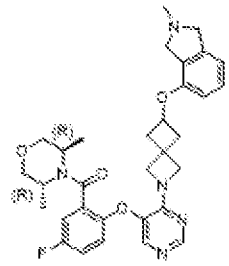
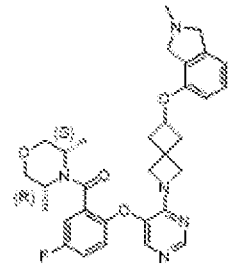
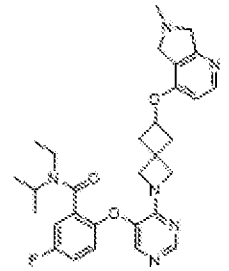
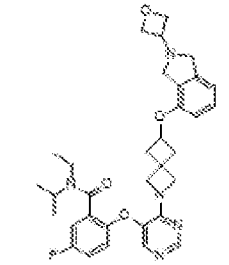
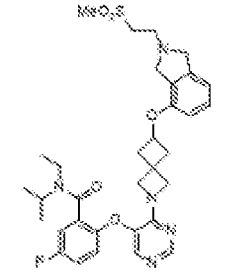
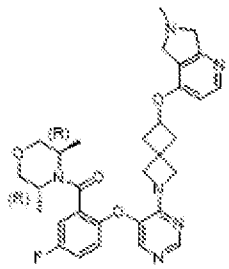
Table 1. Representative Compounds of the Present Disclosure

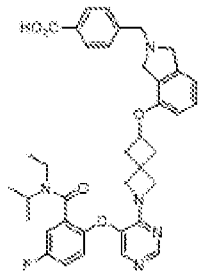
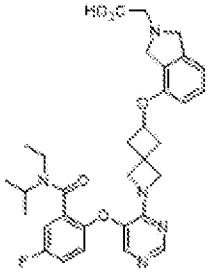
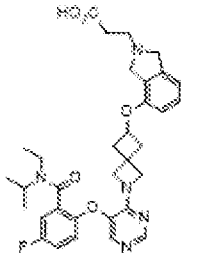
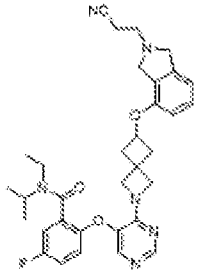
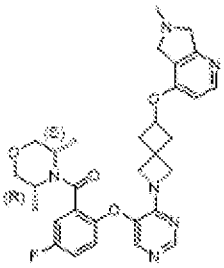
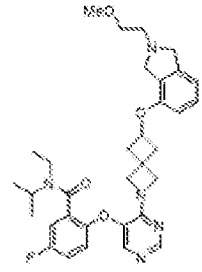
Compound No.	Structure	IUPAC Name
1		*N*-Ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide
2		2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
3		5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N,N-diisopropylbenzamide
4		2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
5		((3R,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
6		5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N,N-diisopropylbenzamide

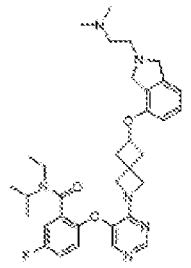
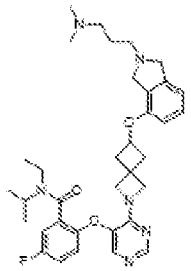
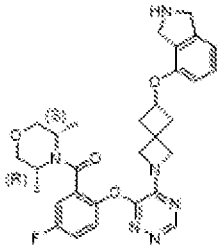
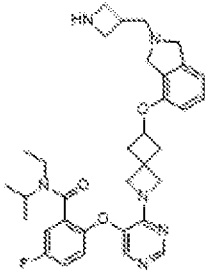
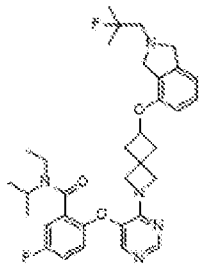
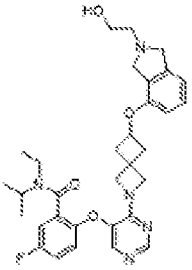
7		*N*-Ethyl-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide
8		((3S,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
9		(R)-(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)(3-methylmorpholino)methanone
10		((3R,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone
11		N-(2,2-difluoroethyl)-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide
12		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

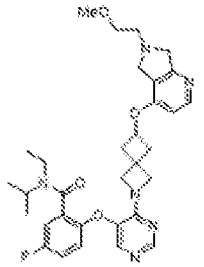
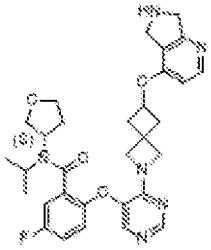
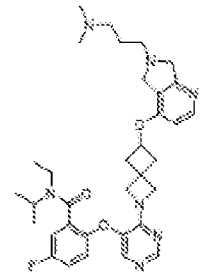
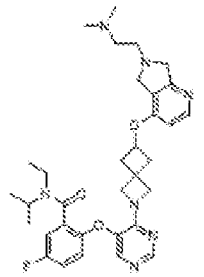
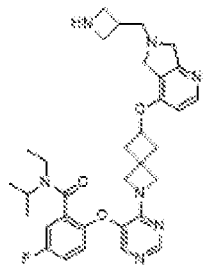
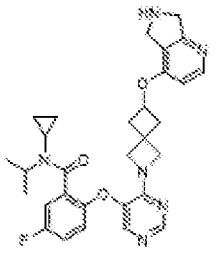
13		2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
14		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
15		N-(2,2-difluoroethyl)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
16		2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide
17		2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
18		(E)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-(2-fluorovinyl)-N-isopropylbenzamide

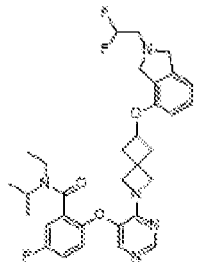
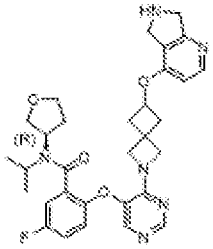
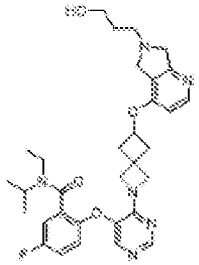
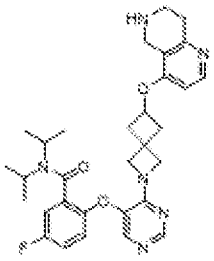
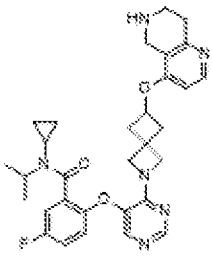
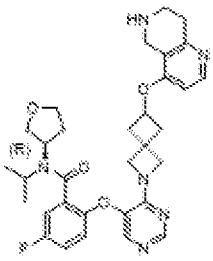
19		5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*,*N*-diisopropylbenzamide
20		*N*-Ethyl-5-fluoro-2-((4-(6-(isoindolin-4-ylamino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide
21		(2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3S,5R)-3,5-dimethylmorpholino)methanone
22		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
23		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
24		(2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3R,5R)-3,5-dimethylmorpholino)methanone

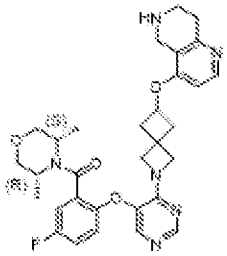
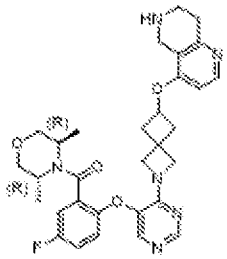
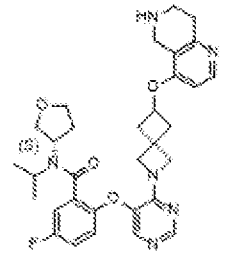
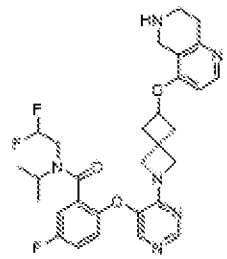
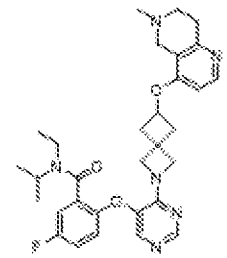
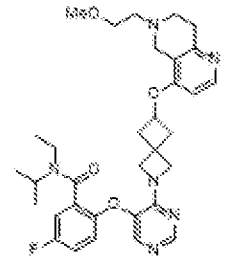
25		((3R,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
26		((3S,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
27		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
28		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((2-(oxetan-3-yl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
29		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((2-(2-(methylsulfonyl)ethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
30		((3R,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone

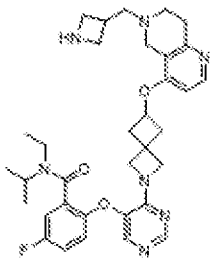
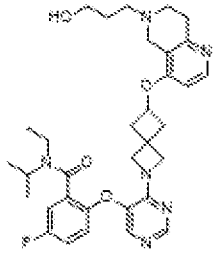
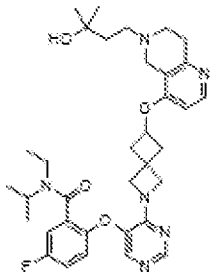
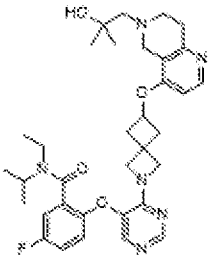
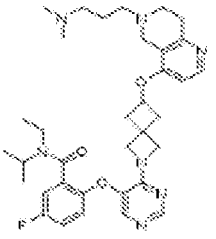
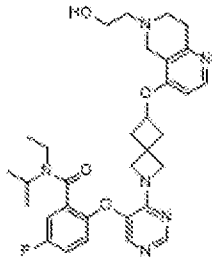
31		4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoic acid
32		2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetic acid
33		3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoic acid
34		2-((4-(6-((2-(2-cyanoethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
35		((3S,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
36		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((2-(2-methoxyethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

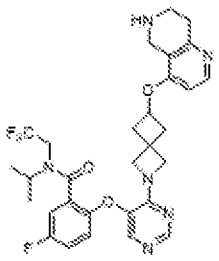
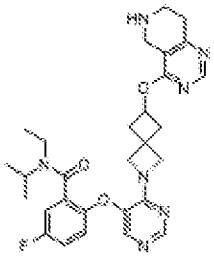
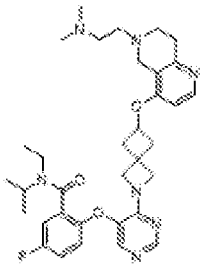
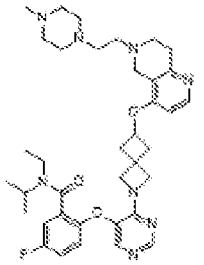
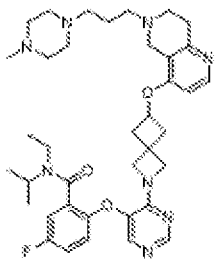
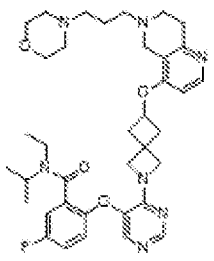
37		2-((4-(6-((2-(2-(dimethylamino)ethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
38		2-((4-(6-((2-(3-(dimethylamino)propyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
39		((3S,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone
40		2-((4-(6-((2-(azetidin-3-ylmethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
41		N-ethyl-5-fluoro-2-((4-(6-((2-(2-fluoro-2-methylpropyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
42		N-ethyl-5-fluoro-2-((4-(6-((2-(2-hydroxyethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

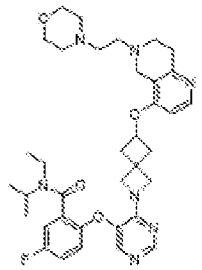
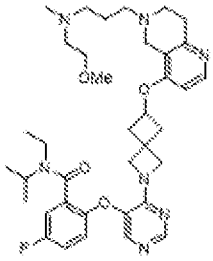
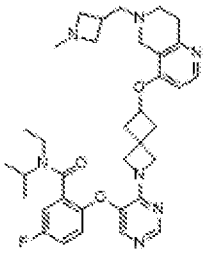
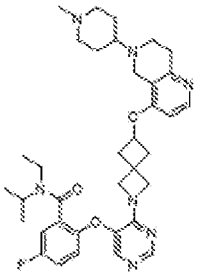
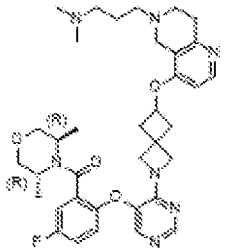
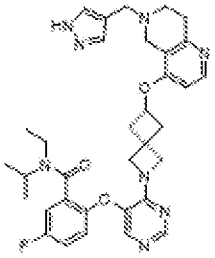
43		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-methoxyethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
44		(S)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydrofuran-3-yl)benzamide
45		2-((4-(6-((6-(3-(Dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
46		2-((4-(6-((6-(2-(dimethylamino)ethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
47		2-((4-(6-((6-(azetidin-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
48		N-cyclopropyl-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide

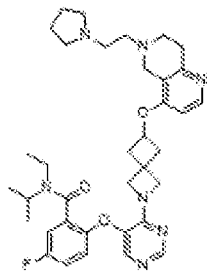
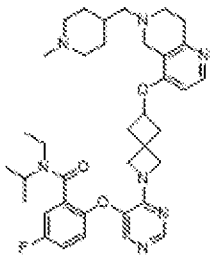
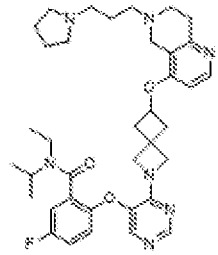
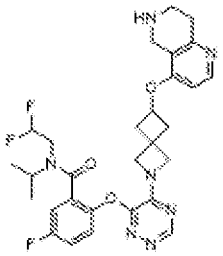
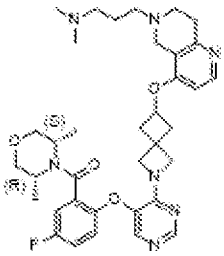
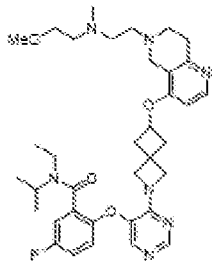
49		2-((4-(6-((2-(2,2-difluoroethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
50		(R)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydrofuran-3-yl)benzamide
51		N-ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxypropyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
52		5-fluoro-N,N-diisopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
53		N-cyclopropyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
54		(R)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydrofuran-3-yl)benzamide

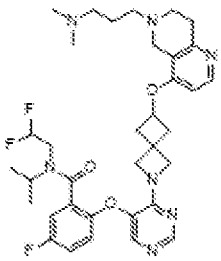
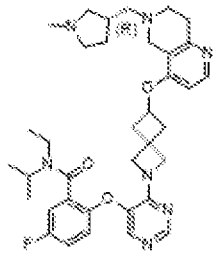
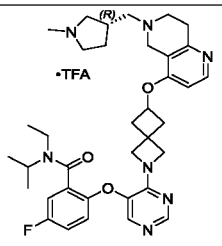
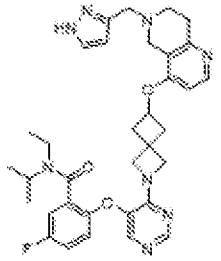
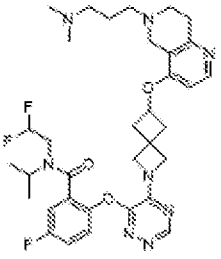
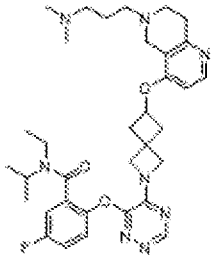
55		((3R,5S)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
56		((3R,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone
57		(S)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydrofuran-3-yl)benzamide
58		*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
59		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
60		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-methoxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

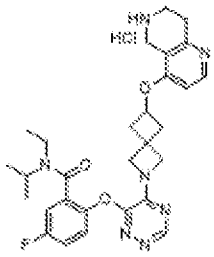
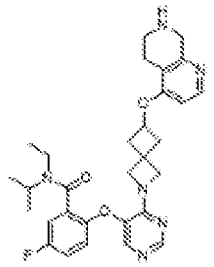
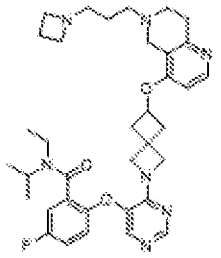
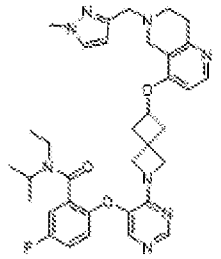
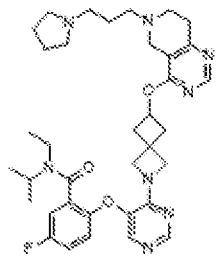
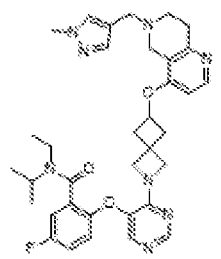
61		2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
62		N-ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
63		N-ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxy-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
64		N-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-2-methylpropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
65		2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
66		N-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

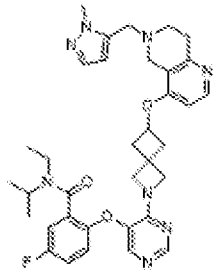
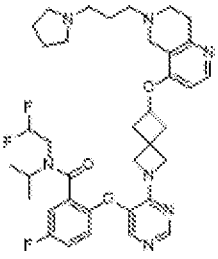
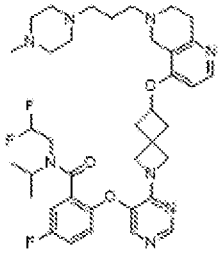
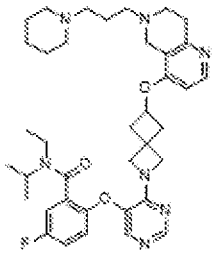
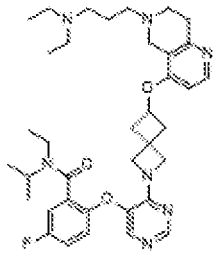
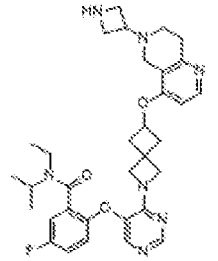
67		5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide
68		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
69		2-((4-(6-((6-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
70		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(4-methylpiperazin-1-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
71		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
72		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-morpholinopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

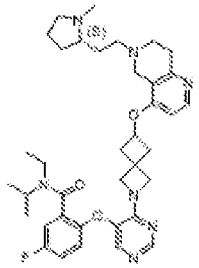
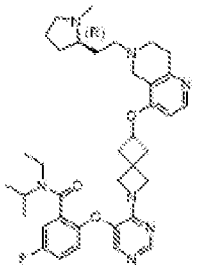
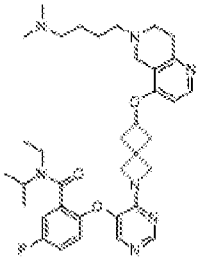
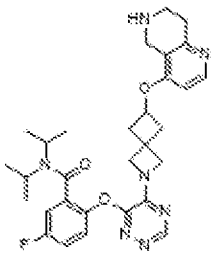
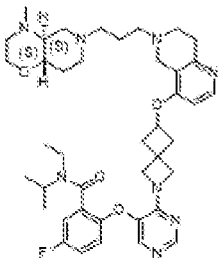
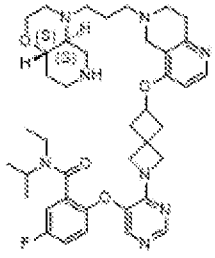
73		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-morpholinoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
74		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((2-methoxyethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
75		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
76		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(1-methylpiperidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
77		(2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3R,5R)-3,5-dimethylmorpholino)methanone
78		2-((4-(6-((6-((1H-pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

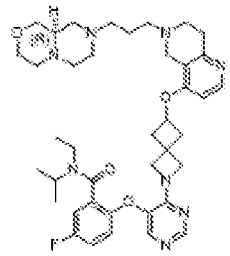
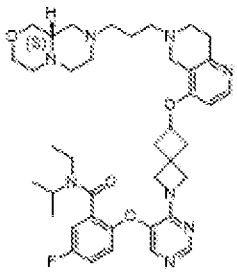
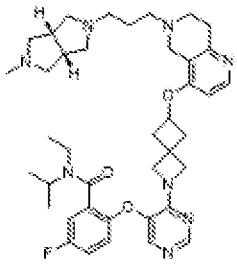
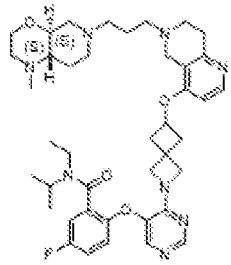
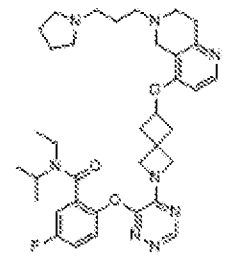
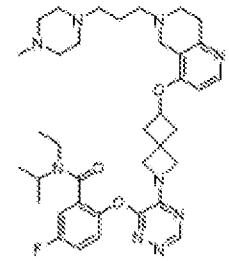
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80		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpiperidin-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
81		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
82		*N*-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
83		(2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3R,5S)-3,5-dimethylmorpholino)methanone
84		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-((2-methoxyethyl)(methyl)amino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

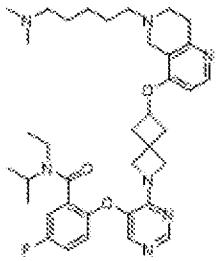
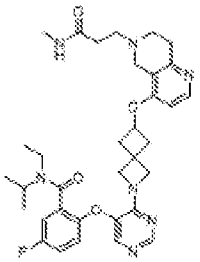
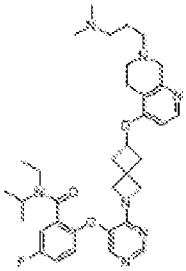
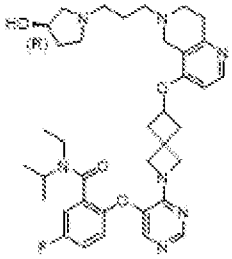
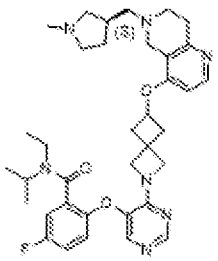
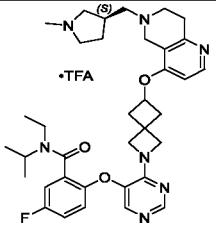
85		*N*-(2,2-Difluoroethyl)-2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide
86		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
86-a		(R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate
87		2-((4-(6-((6-((1H-Pyrazol-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
88		*N*-(2,2-Difluoroethyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide
89		2-((5-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

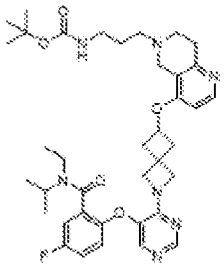
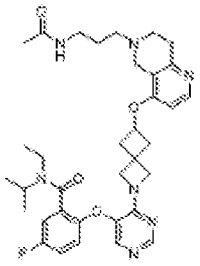
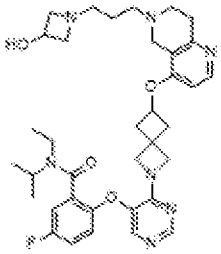
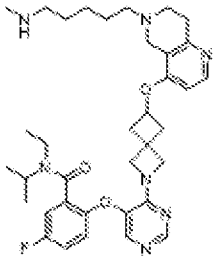
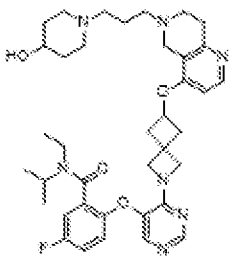
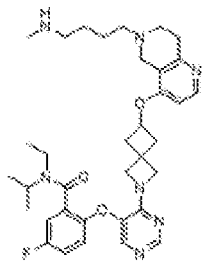
90		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride
91		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
92		2-((4-(6-((6-(3-(Azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
93		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
94		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
95		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

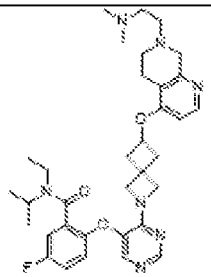
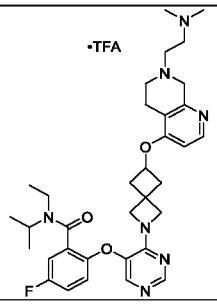
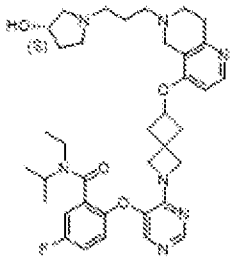
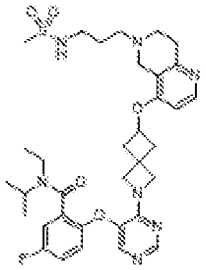
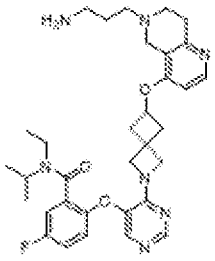
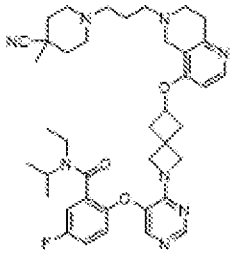
96		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-5-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
97		N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
98		N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
99		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(piperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
100		2-((4-(6-((6-(3-(diethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
101		2-((4-(6-((6-(azetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

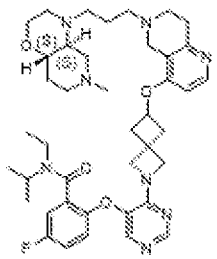
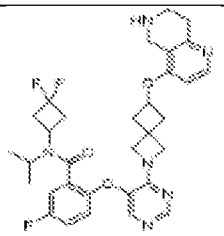
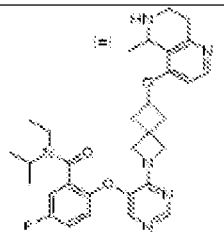
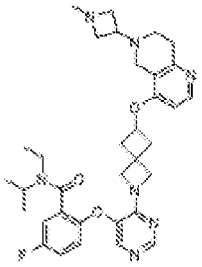
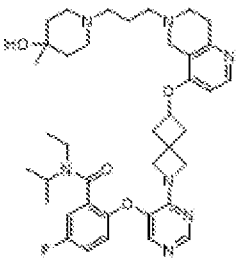
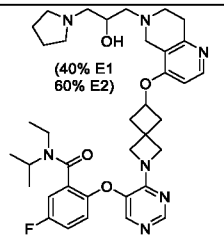
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103		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
104		2-((4-(6-((6-(4-(dimethylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
105		5-fluoro-N,N-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
106		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazin-6(5H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
107		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-octahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

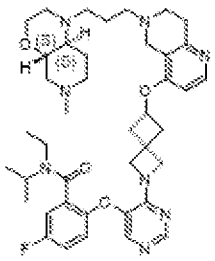
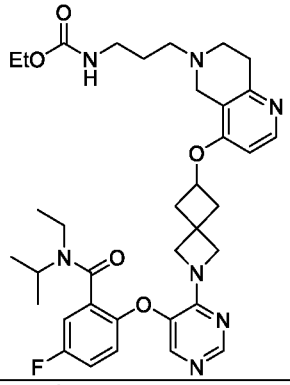
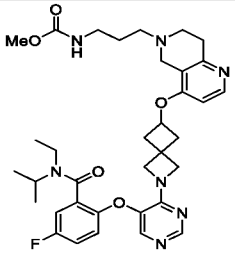
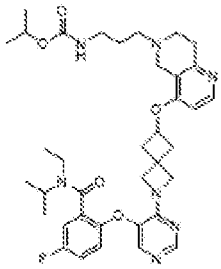
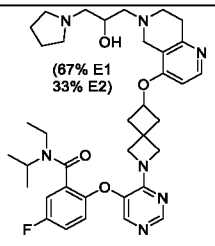
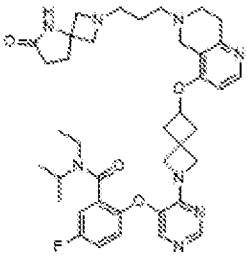
108		(R)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
109		(S)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
110		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
111		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazin-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
112		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
113		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

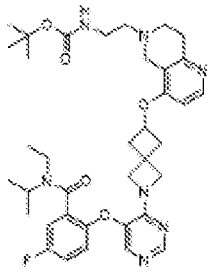
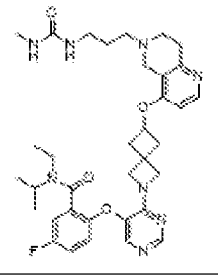
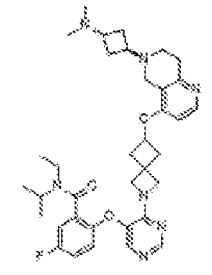
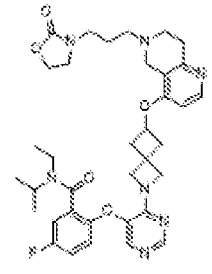
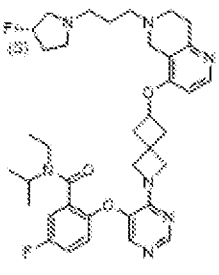
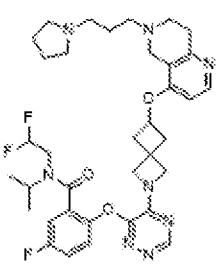
114		2-((4-(6-((6-(5-(dimethylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
115		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(methylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
116		2-((4-(6-((7-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
117		(R)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxypyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
118		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
118-a		(S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate

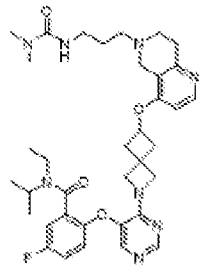
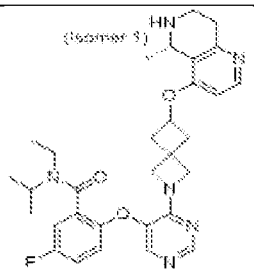
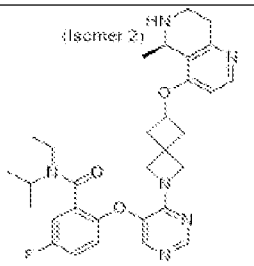
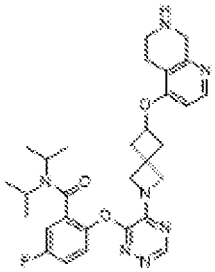
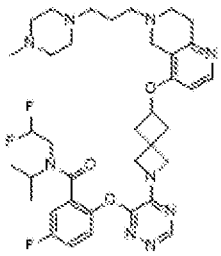
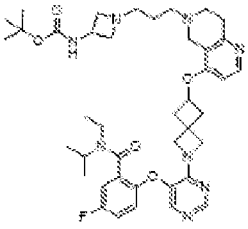
119		tert-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate
120		2-((4-(6-((6-(3-acetamidopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
121		N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxyazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
122		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(5-(methylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
123		N-ethyl-5-fluoro-2-((4-(6-((6-(3-(4-hydroxypiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
124		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

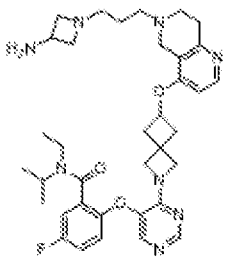
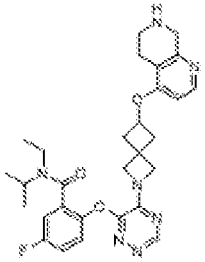
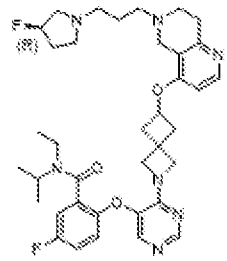
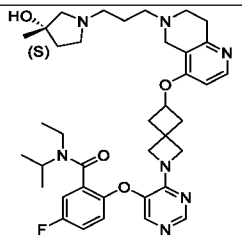
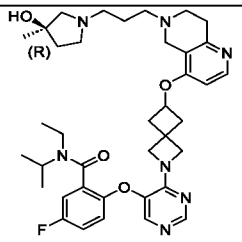
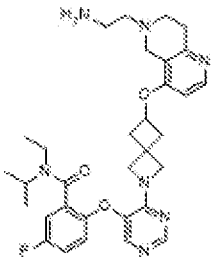
125		2-((4-(6-((7-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
125-a		2-((4-(6-((7-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide 2,2,2-trifluoroacetate
126		(S)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxypyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
127		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(methylsulfonamido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
128		2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
129		2-((4-(6-((6-(3-(4-cyano-4-methylpiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

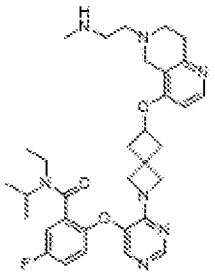
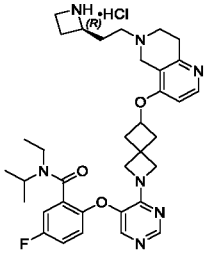
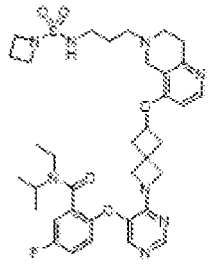
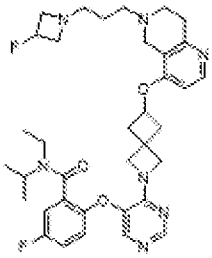
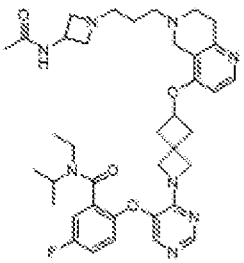
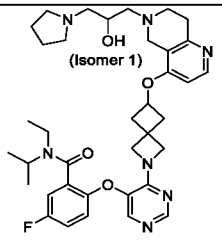
130		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-6-methyloctahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
131		*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
132		(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
133		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(1-methylazetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
134		N-ethyl-5-fluoro-2-((4-(6-((6-(3-(4-hydroxy-4-methylpiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
135		N-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

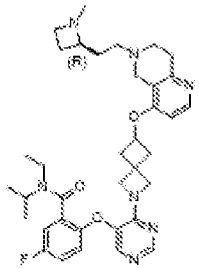
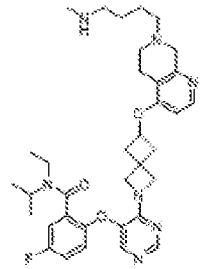
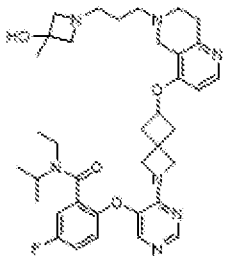
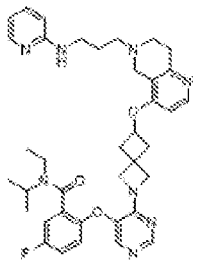
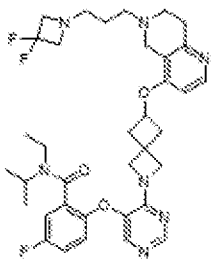
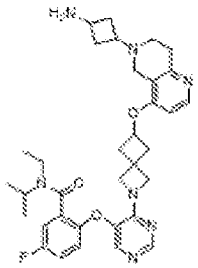
136		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-6-methyloctahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
137		ethyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate
138		methyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate
139		isopropyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate
140		N-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
141		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(6-oxo-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

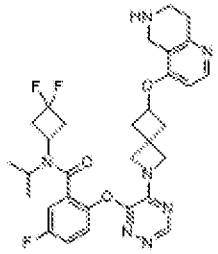
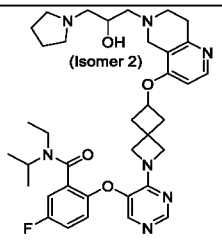
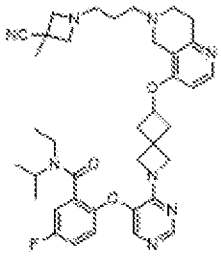
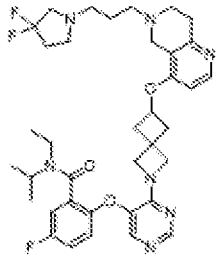
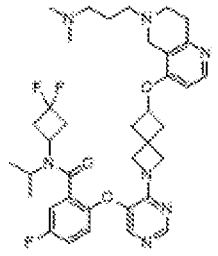
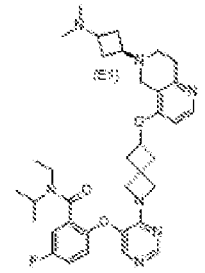
142		tert-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)carbamate
143		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methylureido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
144		2-((4-(6-((6-(3-(dimethylamino)cyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
145		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(2-oxooxazolidin-3-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
146		(S)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
147		N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

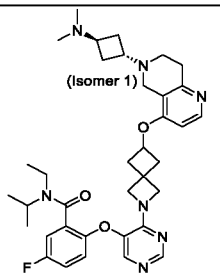
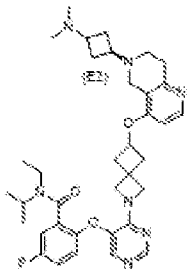
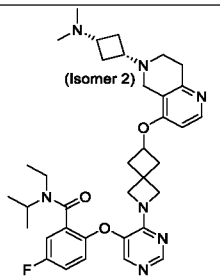
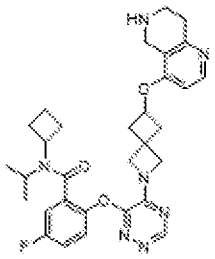
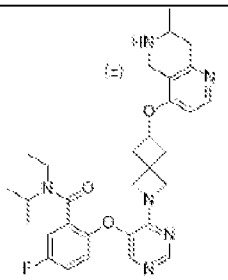
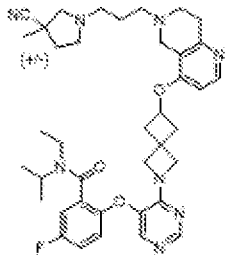
148		2-((4-(6-((6-(3-(3,3-dimethylureido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
149		(*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
150		(*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
151		5-fluoro-N,N-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
152		N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
153		tert-butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate

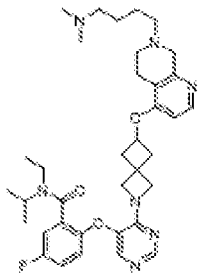
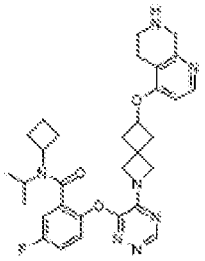
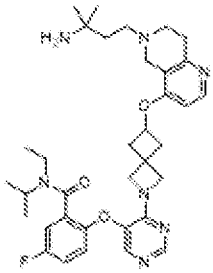
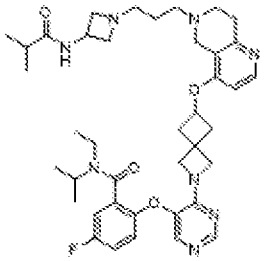
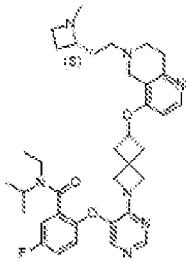
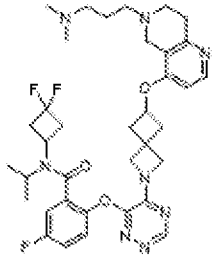
154		2-((4-(6-((6-(3-(3-aminoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
155		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
156		(R)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
157		(S)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
158		(R)-N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
159		2-((4-(6-((6-(2-aminoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

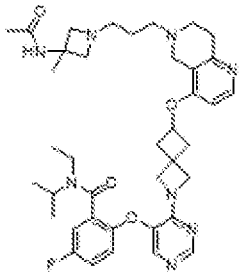
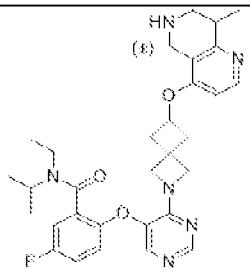
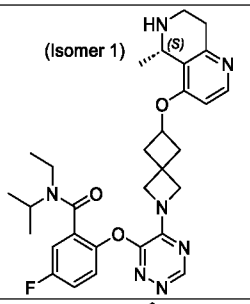
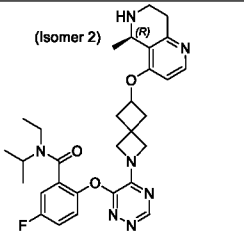
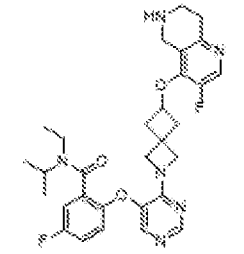
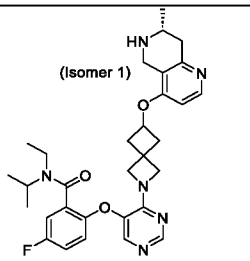
160		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
161		(R)-2-((4-(6-((6-(2-(azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide dihydrochloride
162		2-((4-(6-((6-(3-(azetidine-1-sulfonamido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
163		N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoroazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
164		2-((4-(6-((6-(3-(3-acetamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
165		(E1)-N-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

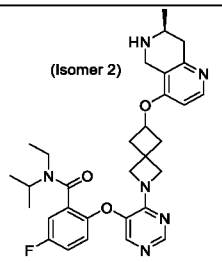
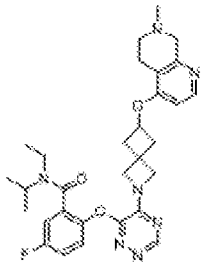
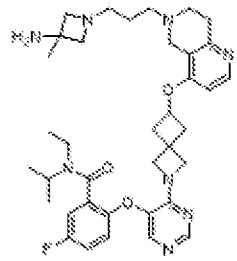
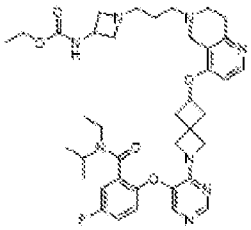
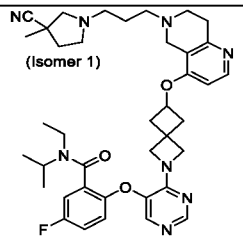
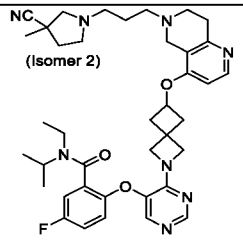
166		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
167		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((7-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
168		N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
169		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(pyridin-2-ylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
170		2-((4-(6-((6-(3-(3,3-difluoroazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
171		2-((4-(6-((6-(3-aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

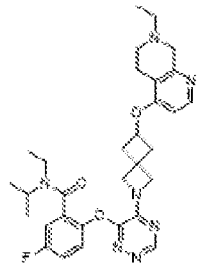
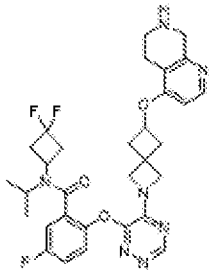
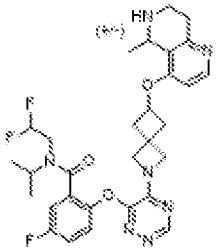
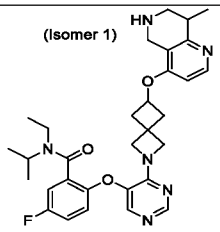
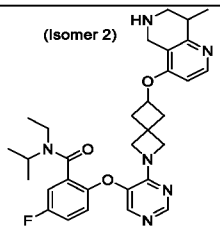
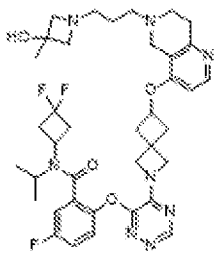
172		*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
173		(E2)-N-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
174		2-((4-(6-((6-(3-(3-cyano-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
175		2-((4-(6-((6-(3-(3,3-difluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
176		*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide
177		(E1)-2-((4-(6-((6-((1r,3r)-3-(dimethylamino)cyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

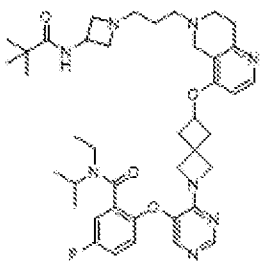
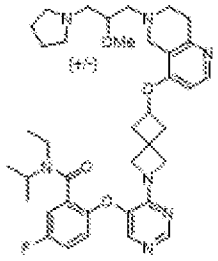
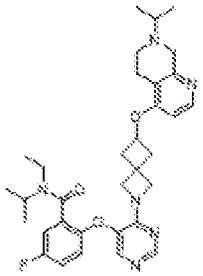
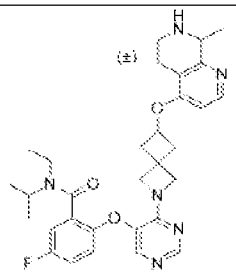
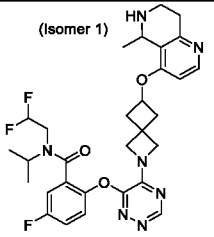
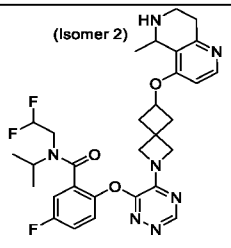
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178		(E2)-2-((4-(6-((6-((1s,3s)-3-(dimethylamino)cyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
178-a		(E2)-2-((4-(6-((6-(3-Aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
179		N-cyclobutyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
180		(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
181		(±)-2-((4-(6-((6-(3-(3-cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

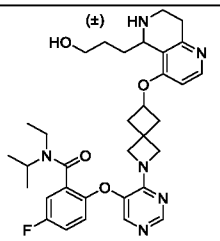
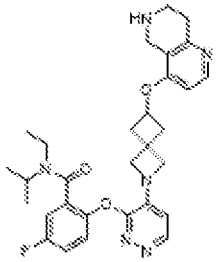
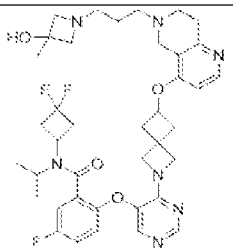
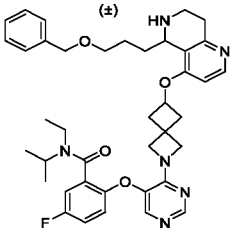
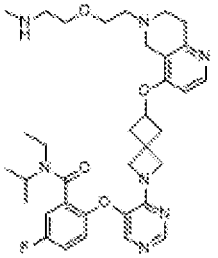
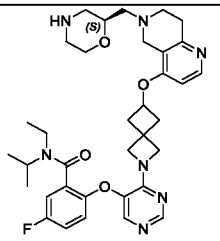
182		2-((4-(6-((7-(4-(dimethylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
183		N-cyclobutyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
184		2-((4-(6-((6-(3-amino-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
185		N-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-isobutyramidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
186		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
187		*N*-(3,3-Difluorocyclobutyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide

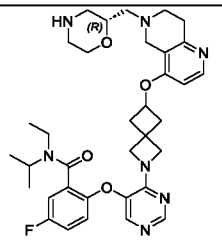
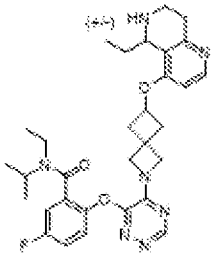
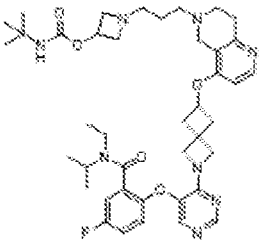
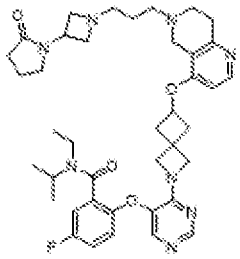
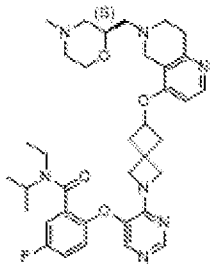
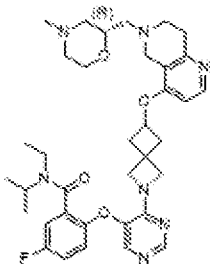
188		2-((4-(6-((6-(3-(3-acetamido-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
189		(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
190		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
191		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
192		N-ethyl-5-fluoro-2-((4-(6-((3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
193		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

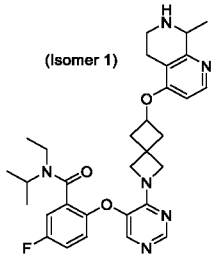
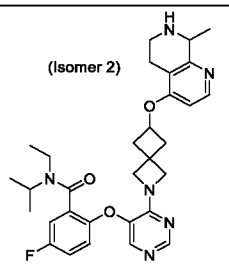
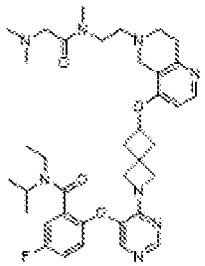
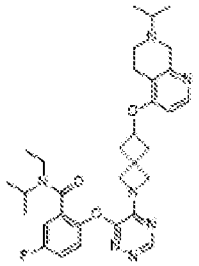
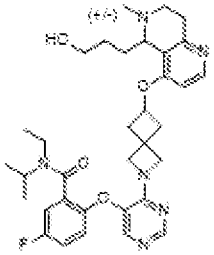
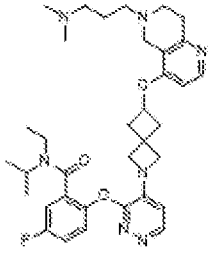
194		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
195		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
196		2-((4-(6-((6-(3-(3-amino-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
197		ethyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate
198		(E1)-2-((4-(6-((6-(3-(3-cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
199		(E2)-2-((4-(6-((6-(3-(3-cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

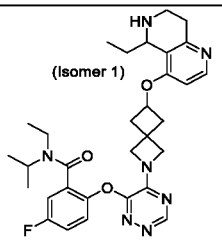
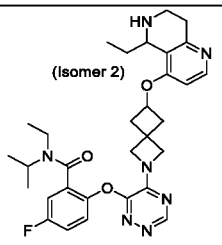
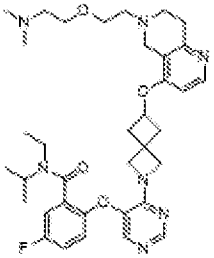
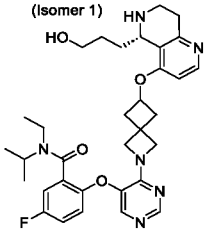
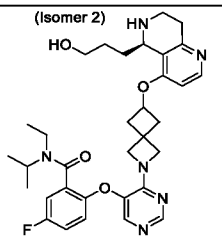
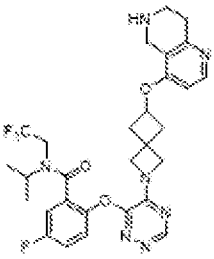
200		N-ethyl-2-((5-(6-((7-ethyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide
201		N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
202		(±)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
203		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
204		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
205		N-(3,3-difluorocyclobutyl)-5-fluoro-2-((5-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide

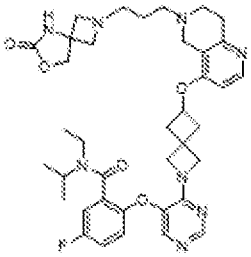
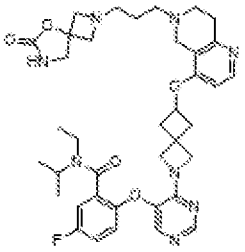
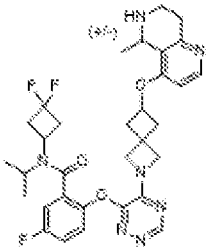
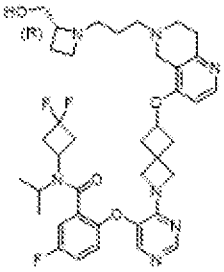
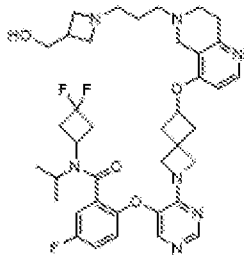
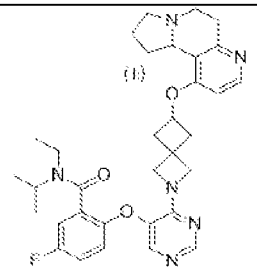
206		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-pivalamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
207		(±)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
208		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
209		(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
210		(E1)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
211		(E2)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

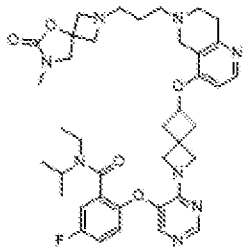
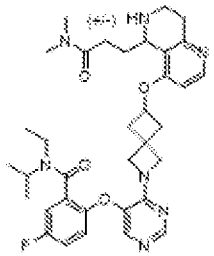
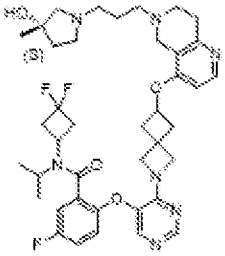
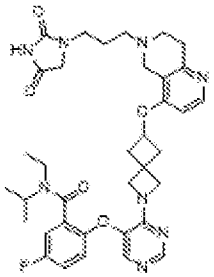
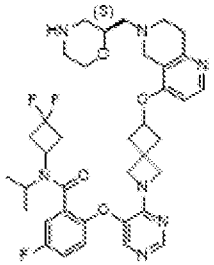
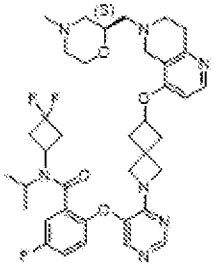
212		(±)-N-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
213		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)benzamide
214		*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide
215		(±)-2-((4-(6-((5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
216		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(2-(methylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
217		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

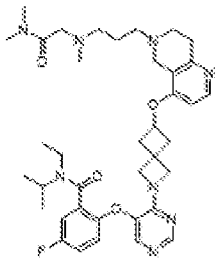
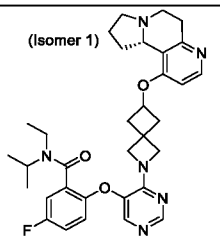
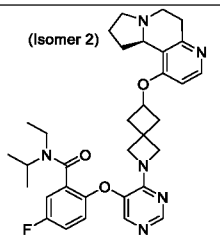
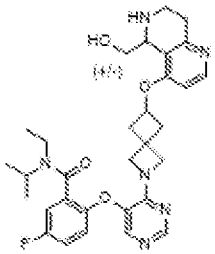
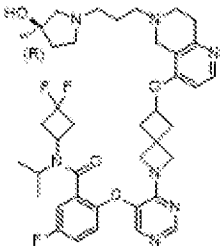
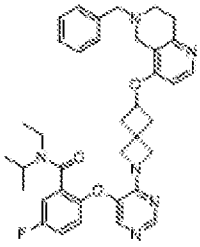
218		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
219		(±)-N-ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide
220		1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl tert-butylcarbamate
221		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-(2-oxopyrrolidin-1-yl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
222		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
223		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

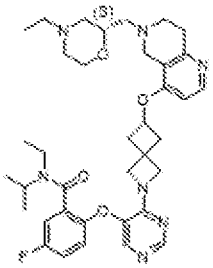
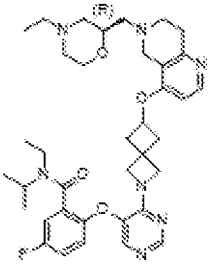
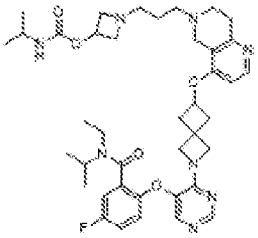
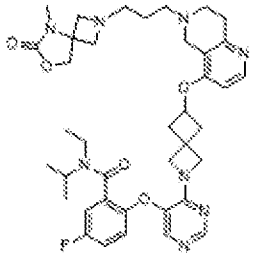
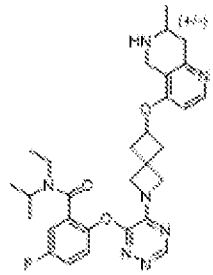
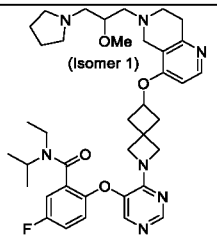
224		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
225		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
226		2-((4-(6-((6-(2-(2-(dimethylamino)-N-methylacetamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
227		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
228		(±)-N-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
229		2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

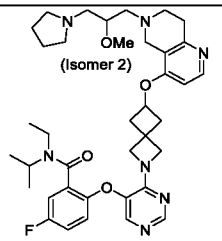
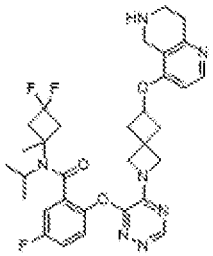
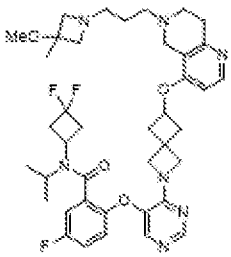
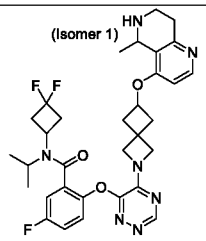
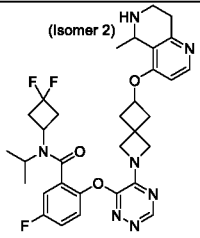
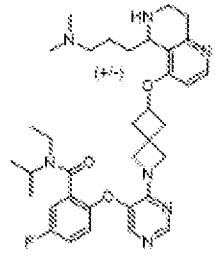
230		(E1)-N-ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide
231		(E2)-N-ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide
232		2-((4-(6-((6-(2-(2-(dimethylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
233		(E1)-N-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
234		(E2)-N-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
235		5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide

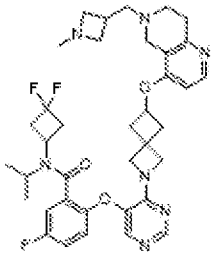
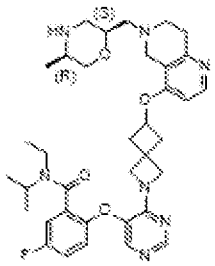
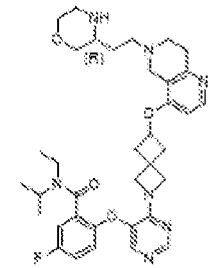
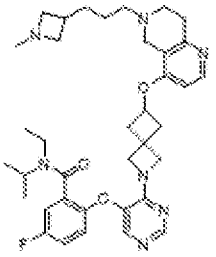
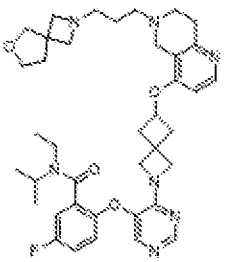
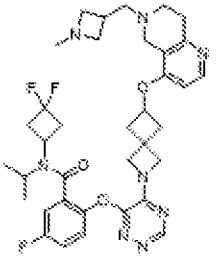
236		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
237		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
238		(±)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
239		(R)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(2-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
240		N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
241		(±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide

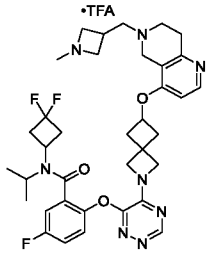
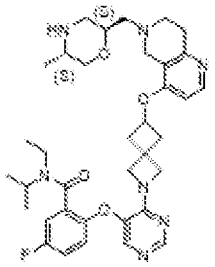
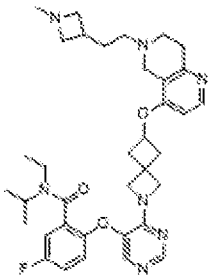
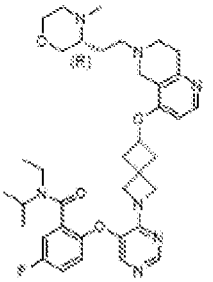
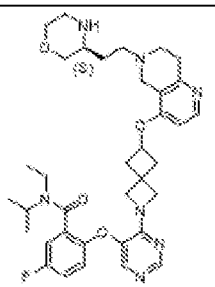
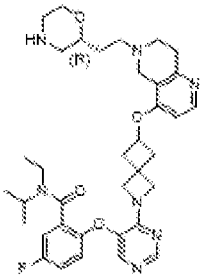
242		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(7-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
243		(±)-2-((4-(6-((5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
244		(S)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
245		2-((4-(6-((6-(3-(2,4-dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
246		(S)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
247		(S)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

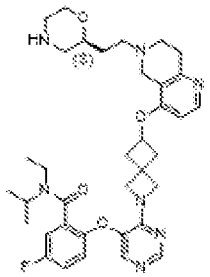
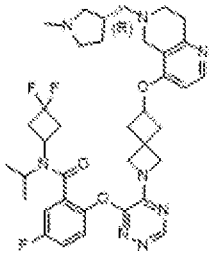
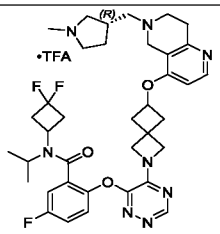
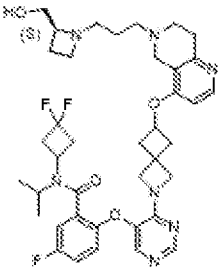
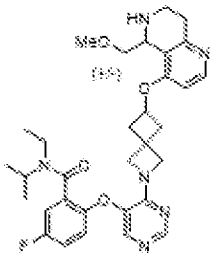
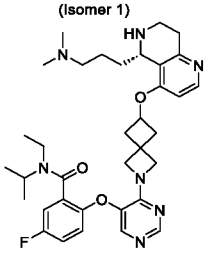
248		2-((4-(6-((6-(3-((2-(dimethylamino)-2-oxoethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
249		(E1)-N-ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
250		(E2)-N-ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
251		(±)-N-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
252		(R)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
253		2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

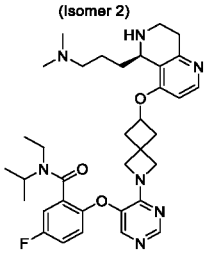
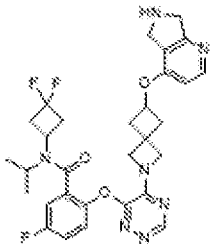
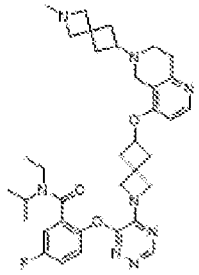
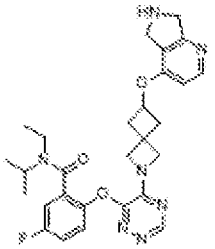
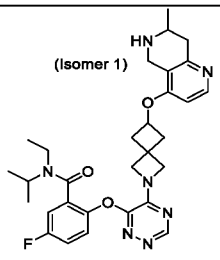
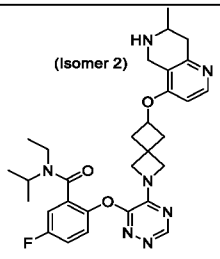
254		(S)-N-ethyl-2-((4-(6-((6-((4-ethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
255		(R)-N-ethyl-2-((4-(6-((6-((4-ethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
256		1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl isopropylcarbamate
257		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
258		(±)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
259		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

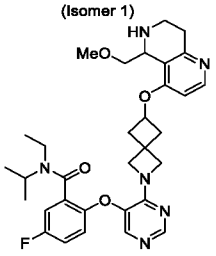
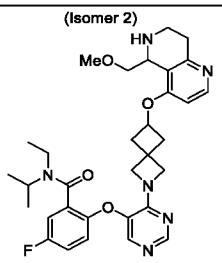
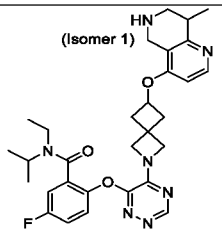
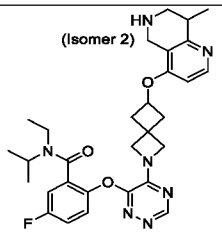
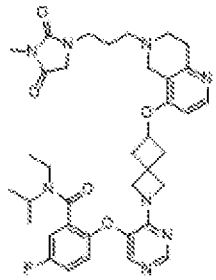
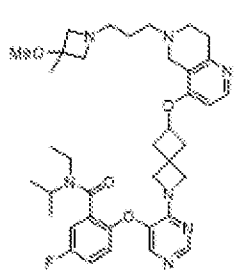
260		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
261		N-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
262		N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
263		(E1)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
264		(E2)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
265		(±)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

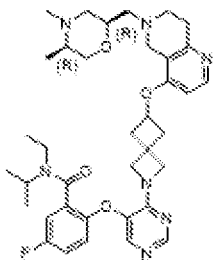
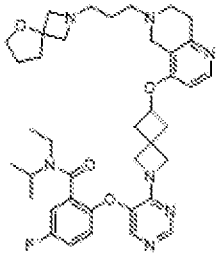
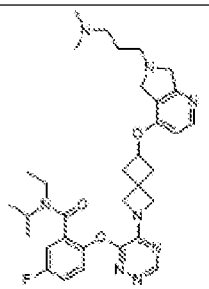
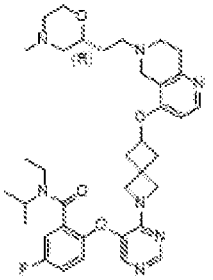
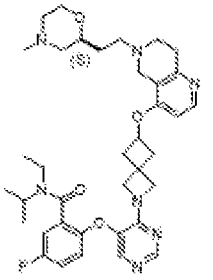
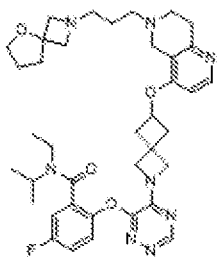
266		N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
267		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(((2S,5R)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
268		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
269		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(1-methylazetidin-3-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
270		2-((4-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
271		N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

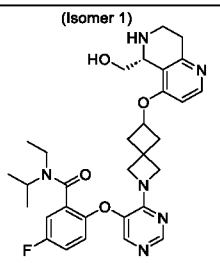
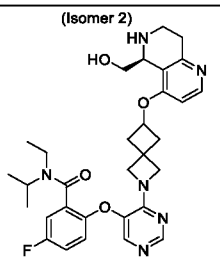
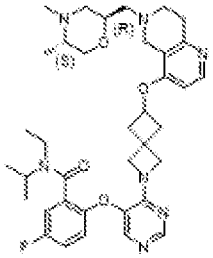
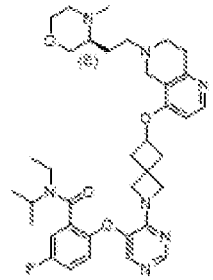
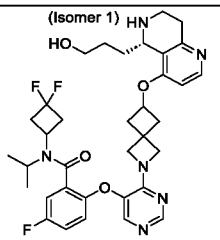
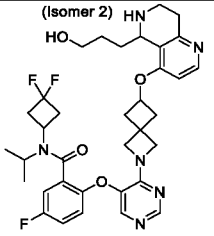
271-a		N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate
272		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(((2S,5S)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
273		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
274		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
275		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
276		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

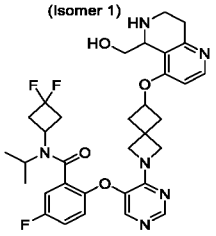
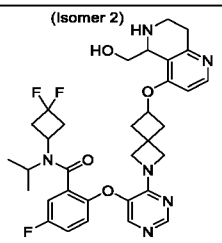
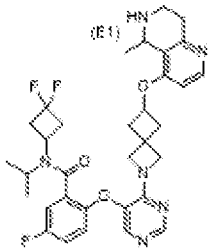
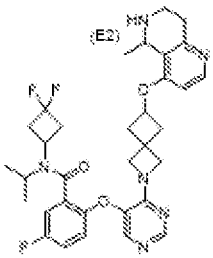
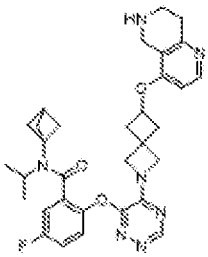
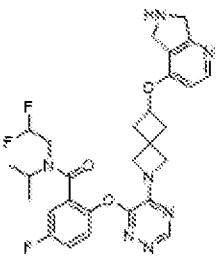
277		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
278		(R)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
278-a		(R)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate
279		(S)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(2-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
280		(±)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
281		(E1)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

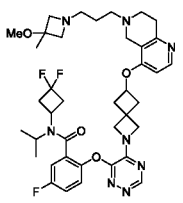
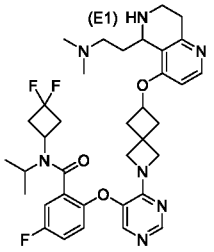
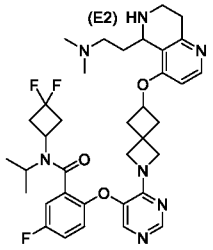
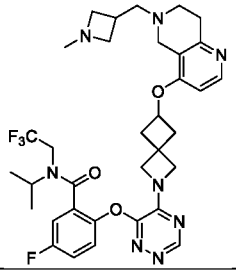
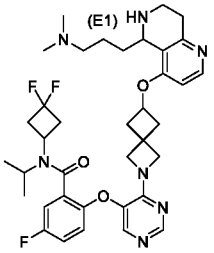
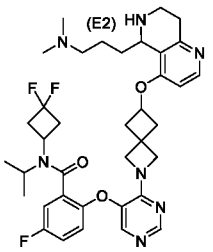
282		(E2)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
283		*N*-(3,3-Difluorocyclobutyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide
284		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
285		2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
286		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
287		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

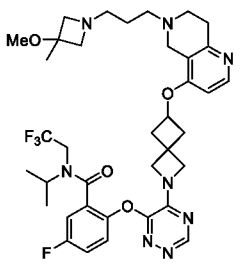
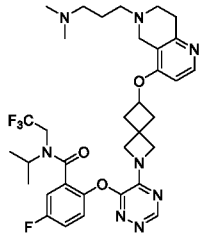
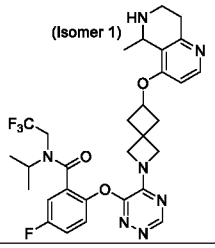
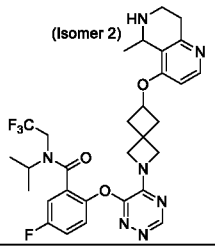
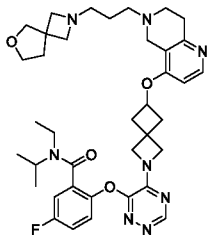
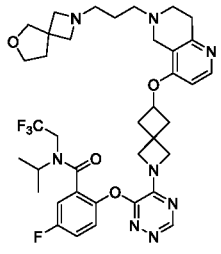
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289		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
290		(E1)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
291		(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
292		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methyl-2,4-dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
293		N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

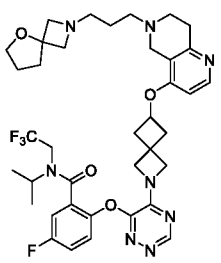
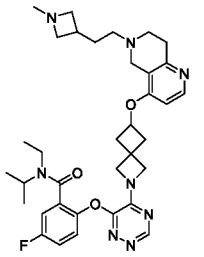
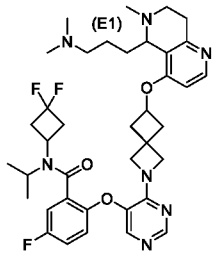
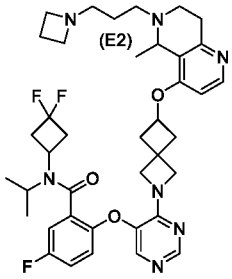
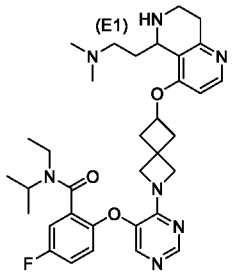
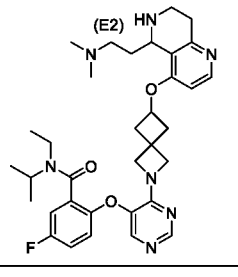
294		2-((4-(6-((6-(((2R,5R)-4,5-dimethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
295		2-((4-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
296		2-((5-(6-((6-(3-(dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
297		(R)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
298		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
299		2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

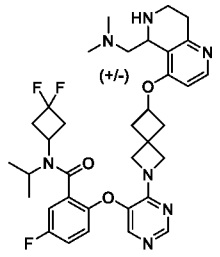
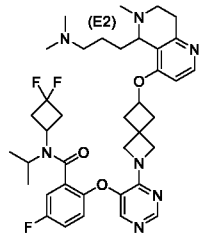
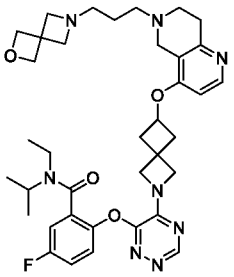
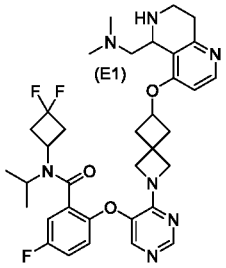
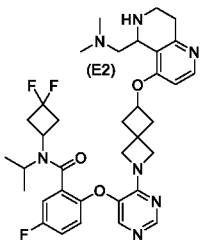
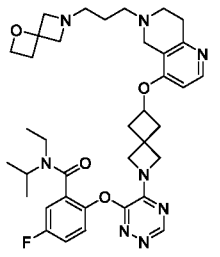
300		(E1)-N-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
301		(E2)-N-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
302		2-((4-(6-((6-(((2R,5S)-4,5-dimethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
303		(S)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
304		(E1)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
305		(E2)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

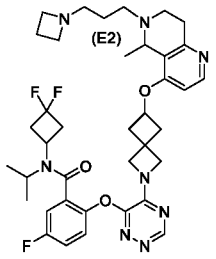
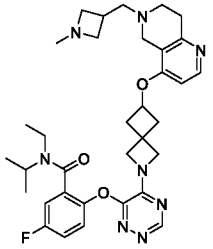
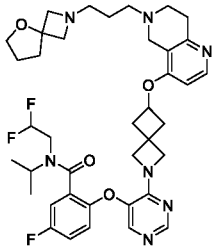
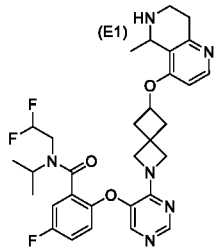
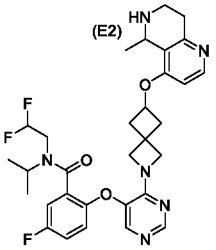
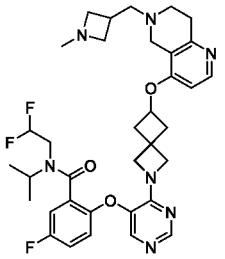
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307		(E2)-N-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide
308		(E1)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
309		(E2)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
310		N-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
311		N-(2,2-difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide

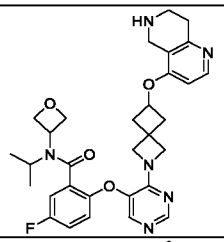
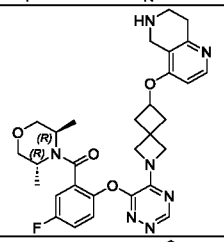
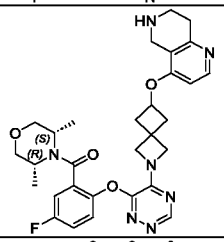
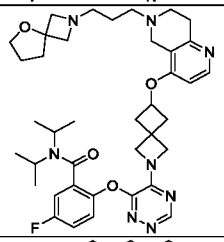
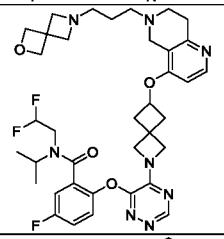
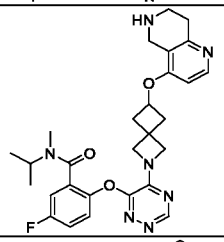
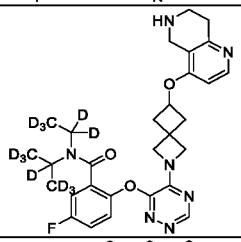
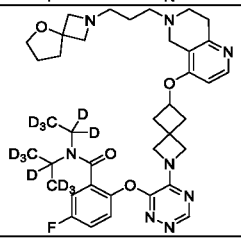
312		N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
313		(E1)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
314		(E2)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
315		5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide
316		(E1)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
317		(E2)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide

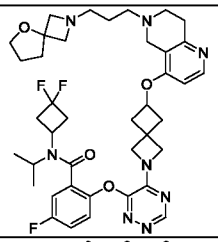
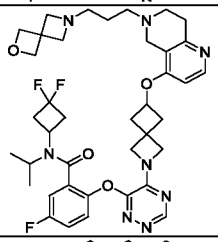
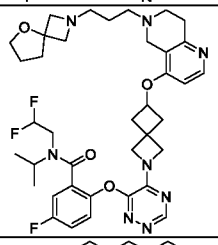
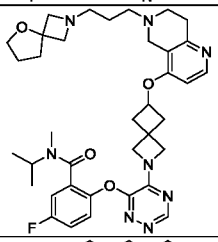
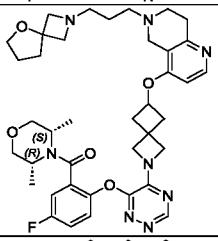
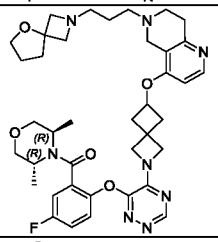
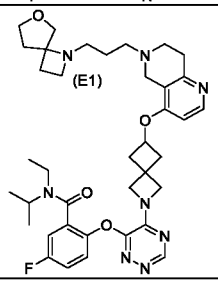
318		5-fluoro-N-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide
319		2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide
320		(E1)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide
321		(E2)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide
322		2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
323		2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide

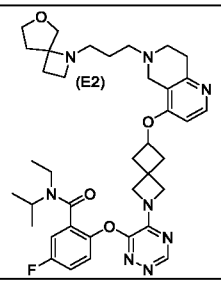
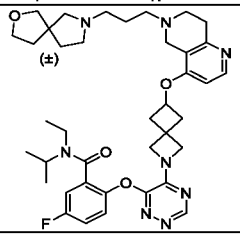
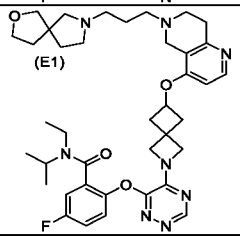
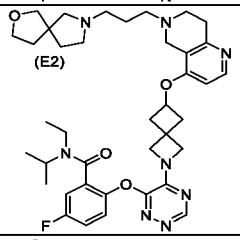
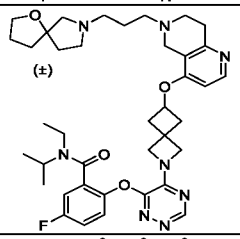
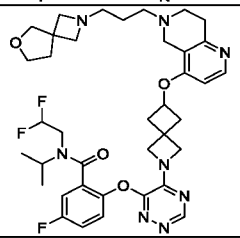
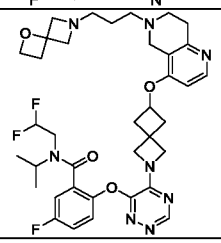
324		2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide
325		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
326		(E1)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
327		(E2)-2-((4-(6-((6-(3-(azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide
328		(E1)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
329		(E2)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

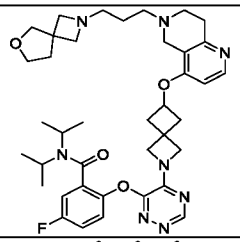
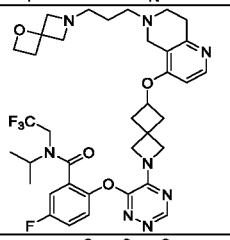
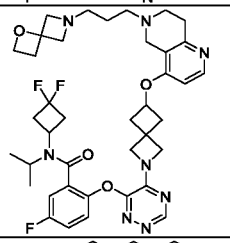
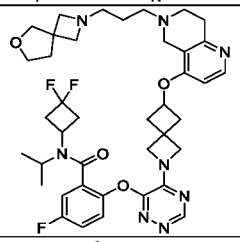
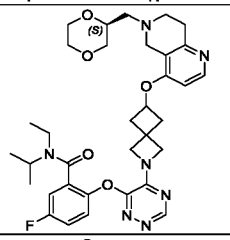
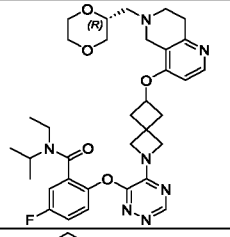
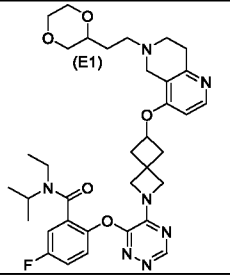
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331		(E2)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
332		2-((5-(6-((6-(3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
333		(E1)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
334		(E2)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide
335		2-((5-(6-((6-(3-(1-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

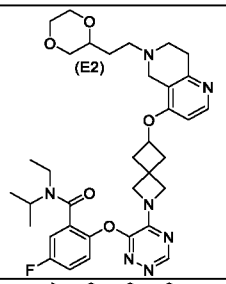
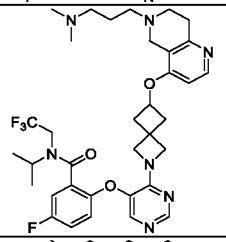
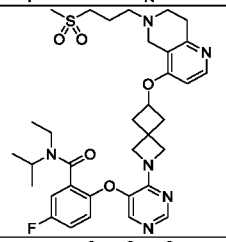
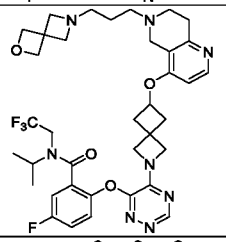
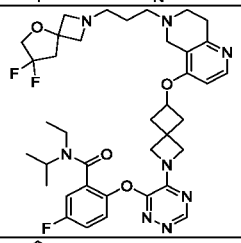
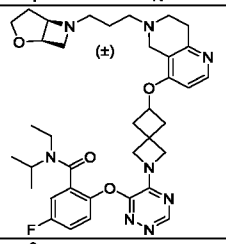
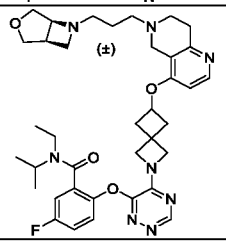
336		(E2)-2-((5-(6-((6-(3-(azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide
337		N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
338		2-((4-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide
339		(E1)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
340		(E2)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
341		N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

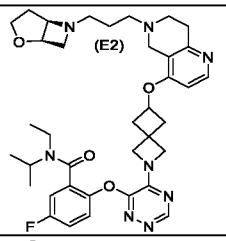
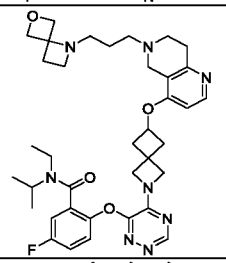
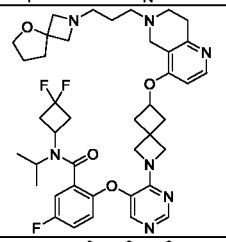
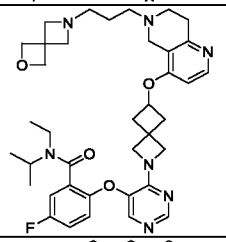
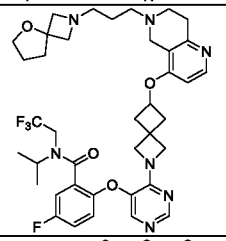
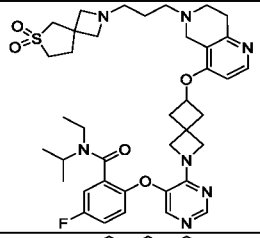
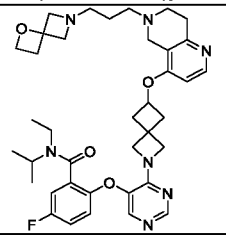
342		5-Fluoro-*N*-isopropyl-N-(oxetan-3-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
343		((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone
344		*3S,5R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone
345		2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide
346		2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide
347		5-Fluoro-*N*-isopropyl-N-methyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
348		*N*-(Ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
349		2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)benzamide

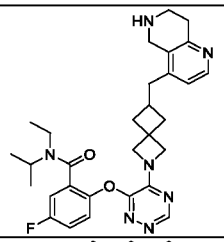
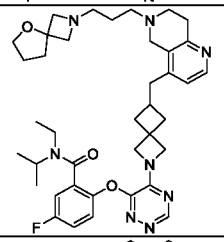
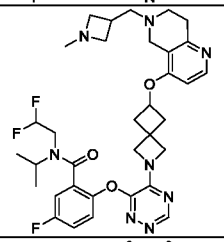
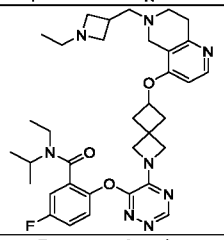
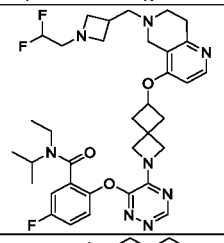
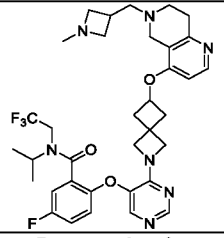
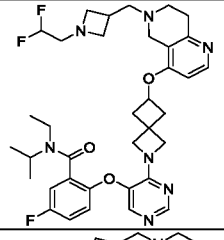
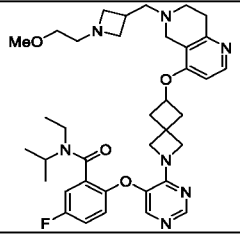
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351		2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide
352		2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide
353		2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide
354		(2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((*3S,5R*)-3,5-dimethylmorpholino)methanone
355		(2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3R,5R)-3,5-dimethylmorpholino)methanone
356		(*E1*)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

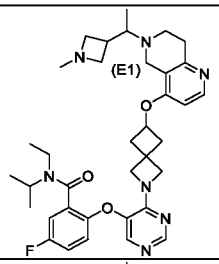
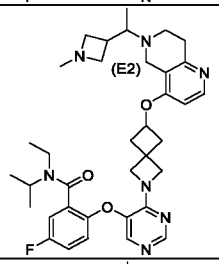
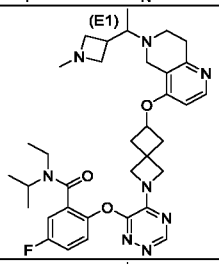
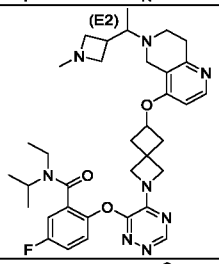
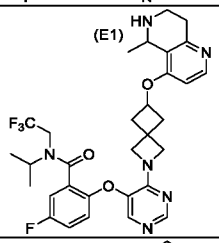
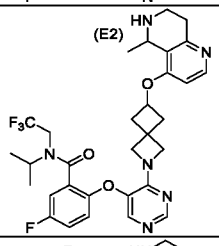
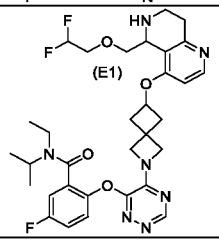
357		(*E2*)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
358		(±)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
359		(*E1*)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
360		(*E2*)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
361		(±)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
362		2-((5-(6-((6-(3-(6-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide
363		2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide

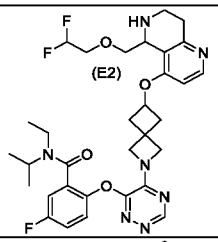
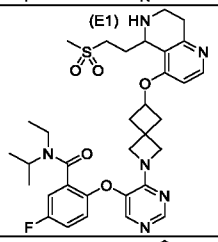
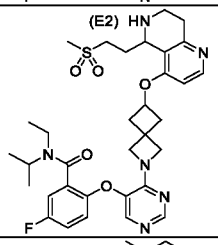
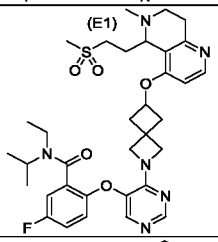
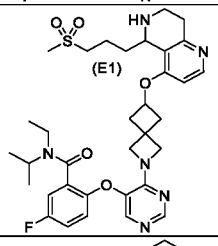
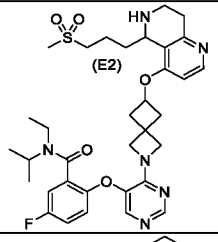
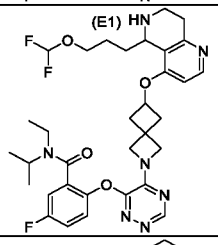
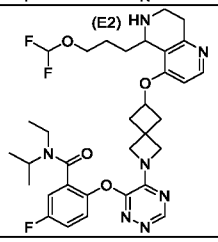
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365		2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide
366		2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide
367		2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide
368		(*S*)-2-((5-(6-((6-((1,4-Dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
369		(*R*)-2-((5-(6-((6-((1,4-Dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
370		(*E1*)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

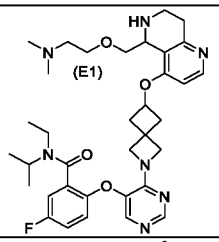
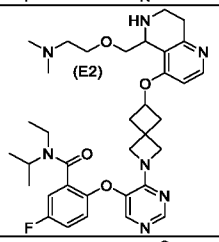
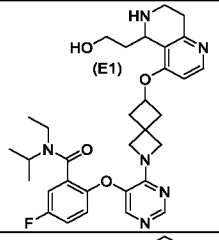
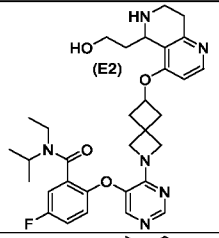
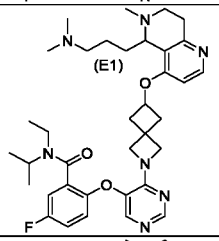
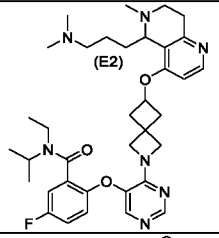
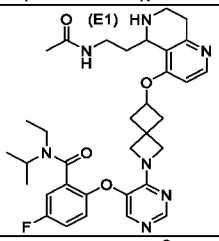
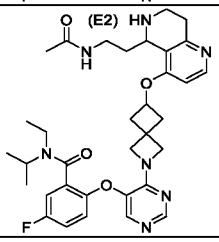
371		(*E2*)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
372		2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide
373		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
374		2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide
375		2-((5-(6-((6-(3-(7,7-Difluoro-5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
376		(±)-2-((5-(6-((6-(3-((1*R*,5*R*)-2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
377		(±)-2-((5-(6-((6-(3-((1*R*,5*S*)-3-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

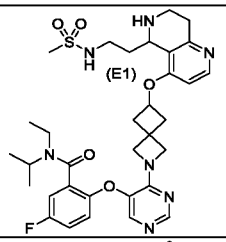
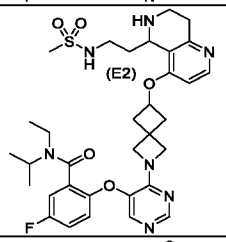
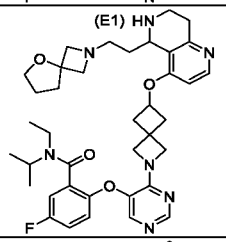
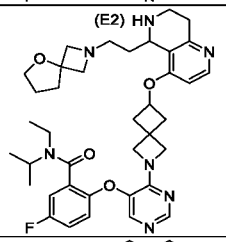
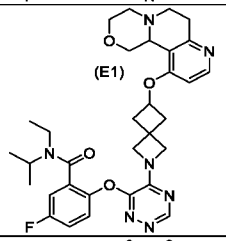
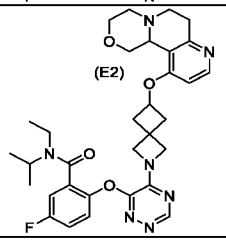
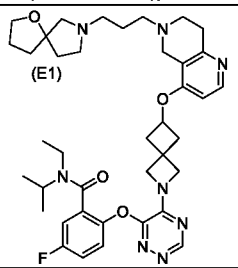
378		*(E2)*-2-((5-(6-((6-(3-((1*R*,5*R*)-2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
379		2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.3]heptan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
380		2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide
381		2-((4-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
382		2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide
383		2-((4-(6-((6-(3-(6,6-Dioxido-6-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
384		2-((4-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

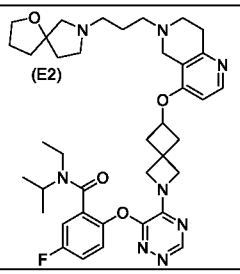
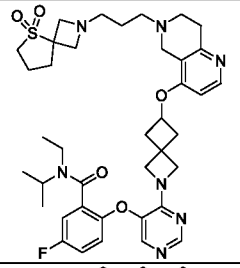
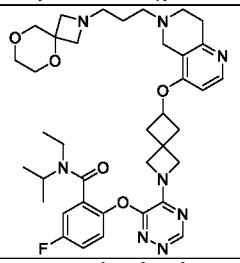
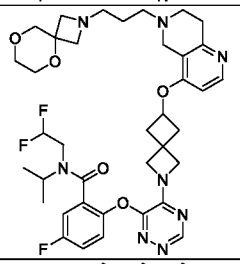
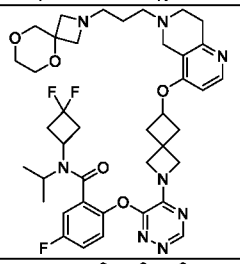
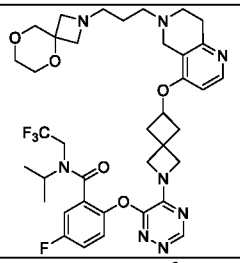
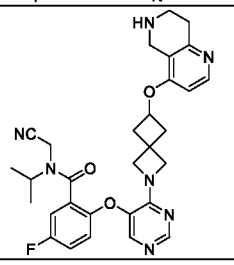
385		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
386		2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
387		*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
388		*N*-Ethyl-2-((5-(6-((6-((1-ethylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide
389		2-((5-(6-((6-((1-(2,2-Difluoroethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
390		5-Fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide
391		2-((4-(6-((6-((1-(2,2-Difluoroethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
392		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-(2-methoxyethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

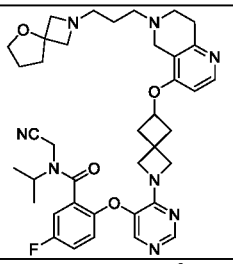
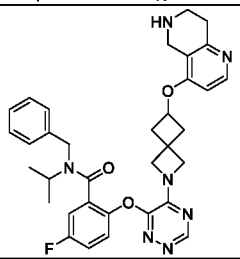
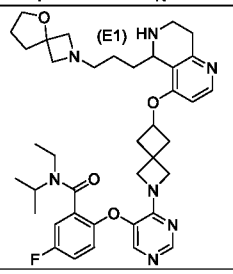
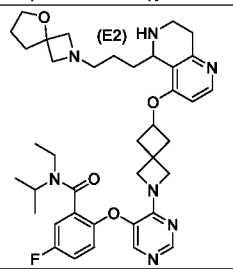
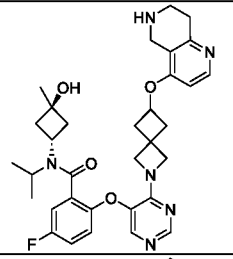
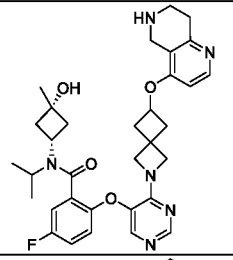
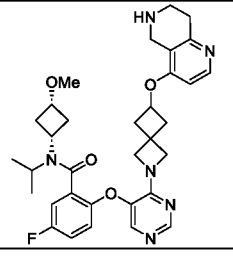
393		(*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
394		(*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
395		(*E1*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
396		(*E2*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
397		(*E1*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide
398		(*E2*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide
399		(*E1*)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

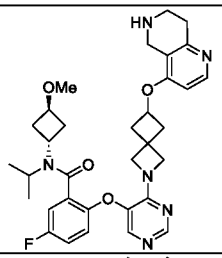
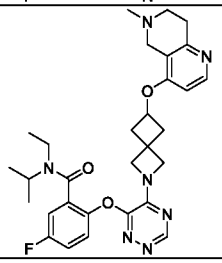
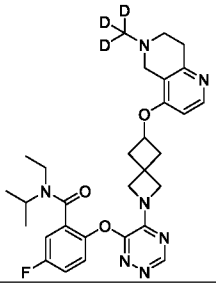
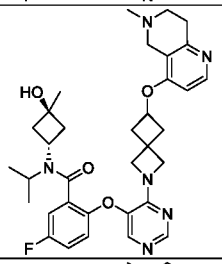
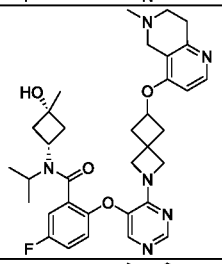
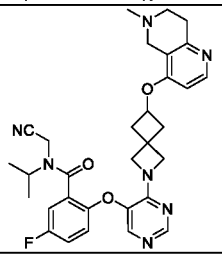
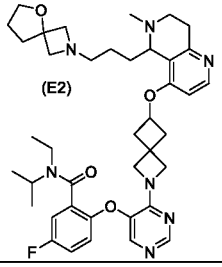
400		(*E2*)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
401		(*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
402		(*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
403		(*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
404		(*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
405		(*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
406		(*E1*)-2-((5-(6-((5-(3-(Difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
407		(*E2*)-2-((5-(6-((5-(3-(Difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

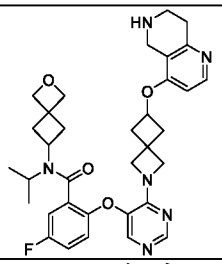
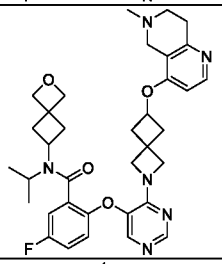
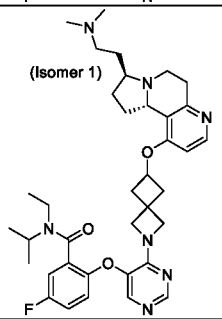
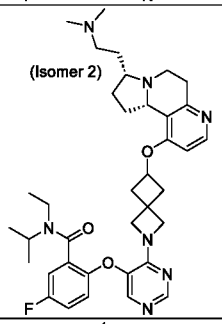
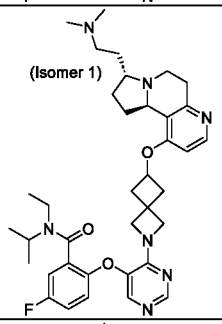
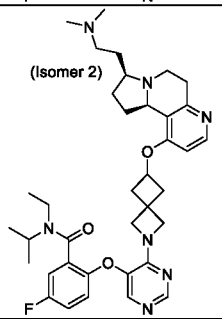
408		(*E1*)-2-((4-(6-((5-((2-(Dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
409		(*E2*)-2-((4-(6-((5-((2-(Dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
410		(*E1*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide
411		(*E2*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide
412		(*E1*)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
413		(*E2*)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
414		(*E1*)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
415		(*E2*)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

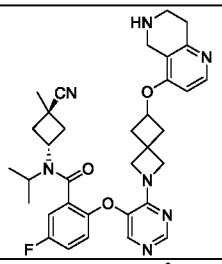
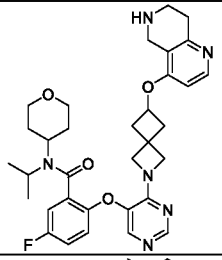
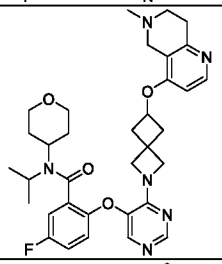
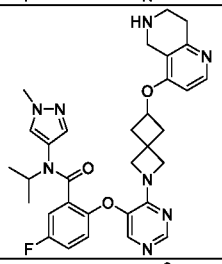
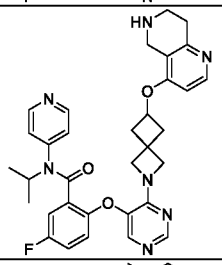
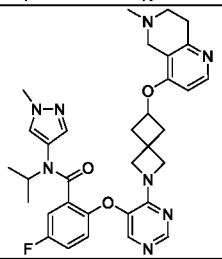
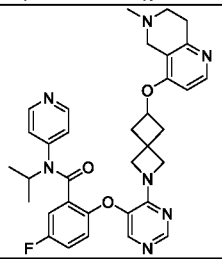
416		(*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
417		(*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
418		(*E1*)-2-((4-(6-((5-(2-(5-Oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
419		(*E2*)-2-((4-(6-((5-(2-(5-Oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
420		(*E1*)-*N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide
421		(*E2*)-*N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide
422		(*E1*)-2-((5-(6-((6-(3-(1-Oxa-7-Azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

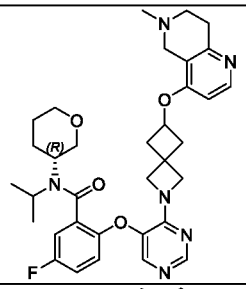
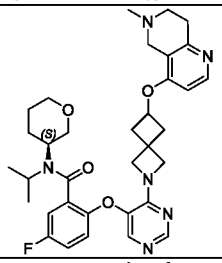
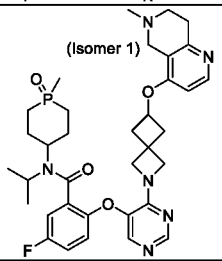
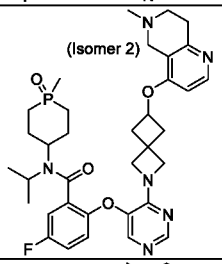
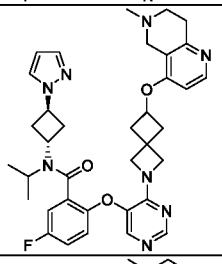
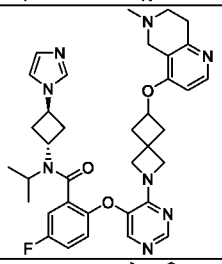
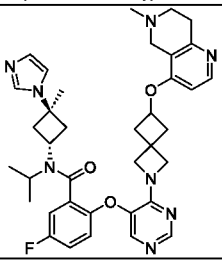
423		(*E2*)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
424		2-((4-(6-((6-(3-(5,5-Dioxido-5-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
425		2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
426		2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide
427		2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide
428		2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide
429		*N*-(Cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

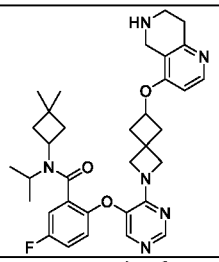
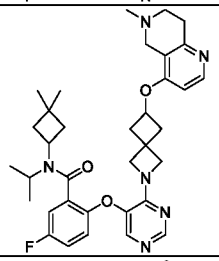
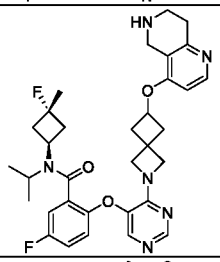
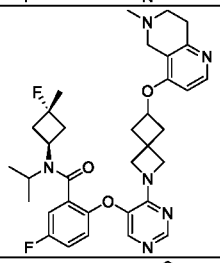
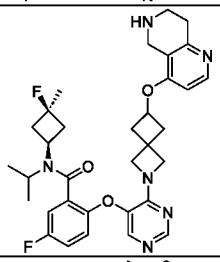
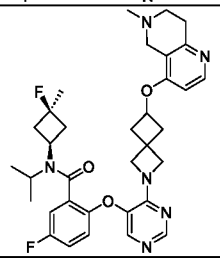
430		2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(cyanomethyl)-5-fluoro-*N*-isopropylbenzamide
431		*N*-Benzyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
432		(*E1*)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
433		(*E2*)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
434		5-Fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
435		5-Fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
436		5-Fluoro-*N*-isopropyl-*N*-((1*s*,3*s*)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

437		5-Fluoro-*N*-isopropyl-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
438		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
439		*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(methyl-d3)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide
440		5-Fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
441		5-Fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
442		*N*-(Cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
443		(*E2*)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

444		5-Fluoro-*N*-isopropyl-*N*-(2-oxaspiro[3.3]heptan-6-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
445		5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2-oxaspiro[3.3]heptan-6-yl)benzamide
446		2-((4-(6-(((8*S*,10a*S*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
447		2-((4-(6-(((8*R*,10a*S*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
448		2-((4-(6-(((8*R*,10a*R*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide
449		2-((4-(6-(((8*S*,10a*R*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

450		*N*-((1*r*,3*r*)-3-Cyano-3-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
451		5-Fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide
452		5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide
453		5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
454		5-Fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
455		5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
456		5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(pyridin-4-yl)benzamide

457		(*R*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-3-yl)benzamide
458		(*S*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-3-yl)benzamide
459		(*E1*)-5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
460		(*E2*)-5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
461		*N*-((1*r*,3*r*)-3-(1H-Pyrazol-1-yl)cyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
462		*N*-((1*r*,3*r*)-3-(1*H*-Imidazol-1-yl)cyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
463		*N*-((1*r*,3*r*)-3-(1*H*-Imidazol-1-yl)-3-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

464		*N*-(3,3-Dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
465		*N*-(3,3-Dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
466		5-Fluoro-*N*-((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
467		5-Fluoro-*N*-((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
468		5-Fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide
469		5-Fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

In some embodiments, a compound according to any embodiments herein (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) exhibits an inhibition activity against the binding of menin and MLL. In some embodiments, a compound according to any embodiments herein (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) exhibits an inhibition activity against the binding of menin and

MLL. In some embodiments, a compound according to any embodiments herein e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) exhibits an inhibition activity against the binding of menin and MLL which is useful in the treatment and/or prevention of one or more diseases in which menin and MLL play a role.

In some embodiments, a compound according to any embodiments herein (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) exhibits low hERG binding. In some embodiments, a compound according to any embodiments herein (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) minimizes hERG binding and is useful for the treatment of one or more diseases in which menin and MLL play a role. Without being bound to any theory, one of the primary causes of QT prolongation is thought to be blockage of the hERG potassium channel in cardiac myocytes. In some embodiments, the compounds of the present disclosure (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) do not significantly block the hERG potassium channel.

In some embodiments, the compounds of the present disclosure (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) do not significantly block the hERG potassium channel (e.g., an IC_{50} greater than 1 μM, 5 μM, 10 μM, 15 μM, 20 μM, 25 μM, 30 μM, 35 μM, 40 μM, or 50 μM) as measured by a standard patch clamp hERG assay.

In some embodiments, the compounds of the present disclosure (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) do not significantly block the hERG potassium channel (e.g., a compound of the invention has an IC_{50} greater than 1 μM, 5 μM, 10 μM, 15 μM, 20 μM, 25 μM, 30 μM, 35 μM, 40 μM, or 50 μM for the hERG potassium channel).

In some embodiments and without wishing to be bound to any theory, the present disclosure is directed to inhibitors of the menin-MLL interaction comprising a pyrrolidine moiety (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IId, IIe, IIf, and III, and Table 1) where the pyrrolidine moiety has been found to reduce hERG inhibition.

In some embodiments and without wishing to be bound to any theory, the present disclosure is directed to inhibitors of the menin-MLL interaction comprising a piperidine moiety (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, and III, and Table 1) where the piperidine moiety has been found to reduce hERG inhibition.

In some embodiments and without wishing to be bound to any theory, the present disclosure is directed to inhibitors of the menin-MLL interaction (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) which are resistant to metabolism. In

some embodiments and without wishing to be bound to any theory, the present disclosure is directed to inhibitors of the menin-MLL interaction (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) which are resistant to metabolism, where the metabolites are inhibitors of the hERG potassium channel. In some embodiments and without wishing to be bound to any theory, the present disclosure is directed to inhibitors of the menin-MLL interaction (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) which are resistant to metabolism, where the metabolism decreases the bioavailability of the inhibitor. In some embodiments and without wishing to be bound to any theory, the present disclosure is directed to inhibitors of the menin-MLL interaction (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) which are resistant to metabolism, where the metabolism decreases the bioavailability of the inhibitor and the corresponding metabolites are more effective (e.g., by IC50, etc.) at binding the hERG potassium channel.

In some embodiments, one or more hydrogen atoms in any of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, or III may be replaced with one or more deuterium atoms.

In some embodiments, the pharmaceutically acceptable salt of the compound of Formula I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, or III is a hydrochloride salt or a 2,2,2,trifluoroacetate salt.

Another aspect is an isotopically labeled compound of any of the formulae delineated herein. Such compounds have one or more isotopic atoms (*e.g.*, ^{3}H, ^{2}H, ^{14}C, ^{13}C, ^{18}F, ^{35}S, ^{32}P, ^{125}I, and ^{131}I) introduced into the compound. Such compounds are useful for drug metabolism studies and diagnostics, as well as therapeutic applications. In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1, or a pharmaceutically acceptable salt thereof.

It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

In some embodiments, the deuterium labeled compound has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation),

or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term "deuterium enrichment factor" means the ratio between the deuterium abundance and the natural abundance of a deuterium.

It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

A compound of the present disclosure or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the disclosure. Further, substitution with deuterium (i.e., 2H) may afford certain therapeutic advantages resulting from greater metabolic stability, e.g., increased in vivo half-life or reduced dosage requirements.

For the avoidance of doubt, it is to be understood that, where in this specification a group is qualified by "described herein", the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

Potency can also be determined by IC_{50} value. A compound with a lower IC_{50} value, as determined under substantially similar conditions, is more potent relative to a compound with a higher IC_{50} value.

Potency can also be determined by EC_{50} value. A compound with a lower EC_{50} value, as determined under substantially similar conditions, is more potent relative to a compound with a higher EC_{50} value.

The compounds of the application are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

In another aspect, the application provides a method of synthesizing a compound disclosed herein. The synthesis of the compounds of the application can be found herein and in the Examples below. Other embodiments are a method of making a compound of any of the formulae herein using any one, or combination of, reactions delineated herein. The method can include the use of one or more intermediates or chemical reagents delineated herein.

It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the disclosure which are, for brevity, described

in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, substituents of compounds of the disclosure are disclosed in groups or in ranges. It is specifically intended that the disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

At various places in the present specification various cycloalkyl, and heterocyclyl rings are described. Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term "a pyridine ring" or "pyridinyl" may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

For compounds of the disclosure in which a variable appears more than once, each variable can be a different moiety independently selected from the group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R.

As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intends to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

As used herein, the term "optionally substituted alkyl" refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino,

arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

As used herein, the term “alkoxy” or “alkoxyl” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

As used herein, the term "amino," employed alone or in combination with other terms, refers to a group of formula $–NH_2$. In some embodiments, an amine can be substituted by one or more groups, e.g., -N-(C_1-C_6 alkyl)$_2$. In some embodiments, when two groups are attached to an amine they can be the same or different. Each group is selected independently of each other and can be each independently optionally substituted.

As used herein, the term “halogen” or "halo," employed alone or in combination with other terms, refers to a halogen atom selected from F, Cl, I or Br. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, the halo substituent is F.

The term “haloalkyl” or “haloalkoxyl” refers to an alkyl or alkoxyl substituted with one or more halogen atoms. In some embodiments, the haloalkyl group is fluorinated. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the haloalkyl group is fluoromethyl, difluoromethyl, or trifluoromethyl. In some embodiments, the haloalkyl group is trifluoromethyl. In some embodiments, the haloalkyl group is 2,2,2-trifluoroethyl. In

some embodiments, the haloalkyl group is 2,2-difluoroethyl. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

As used herein, the term "optionally substituted alkenyl" refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

As used herein, the term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkynyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkynyl groups containing three to six carbon atoms. As used herein, "C_2-C_6 alkenylene linker" or "C_2-C_6 alkynylene linker" is intended to include C_2, C_3, C_4, C_5 or C_6 chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C_2-C_6 alkenylene linker is intended to include C_2, C_3, C_4, C_5 and C_6 alkenylene linker groups.

Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

As used herein, the term "cycloalkyl" refers to a saturated or partially unsaturated hydrocarbon monocyclic or polycyclic (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C3-C12, C3-C10, or C3-C8). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl. In the case of polycyclic cycloalkyl, only one of the rings in the cycloalkyl needs to be non-aromatic. In some embodiments, cycloalkyl may optionally contain one or more alkenylene groups as part of the ring structure. Cycloalkyl groups can include mono- or polycyclic ring systems. Polycyclic ring systems can include fused ring systems and spirocycles. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo or pyrido derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. A heterocyclyl group that includes a fused aromatic (*e.g.*, aryl or heteroaryl) moiety can be attached to the molecule through an atom from either the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized to form carbonyl linkages. In some embodiments, cycloalkyl is C_{3-10} cycloalkyl, C_{3-7} cycloalkyl, or C_{5-6} cycloalkyl. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, and the like. Further exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Additional example cycloalkyl groups, where the cycloalkyl group has a fused aryl or heteroaryl moiety, include tetrahydronaphthalen-2-yl, 2,3-dihydro-1H-inden-2-yl; 2,3,4,9-tetrahydro-1H-carbazol-7-yl; 2,6,7,8-tetrahydrobenzo[cd]indazol-4-yl; and 5,6,7,8,9,10-hexahydrocyclohepta[b]indol-3-yl.

As used herein, the term "aryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbon, such as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl, and the like. In some embodiments, aryl is C_{6-10} aryl. In some embodiments, aryl is C_{6-14} aryl. In some embodiments, the aryl group is a naphthalene ring or phenyl ring. In some embodiments, the aryl group is phenyl.

As used herein, the term "heteroaryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic heterocylic moiety, having one or more heteroatom ring members selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl group has 1, 2, 3, or 4 heteroatom ring members. In some embodiments, the heteroaryl group has 1, 2, or 3 heteroatom ring members. In some embodiments, the heteroaryl group has 1 or 2 heteroatom ring members. In some embodiments, the heteroaryl group has 1 heteroatom ring member. In some embodiments, the heteroaryl group is 5- to 10-membered or 5- to 6-membered. In some embodiments, the heteroaryl group is 5-membered. In some embodiments, the heteroaryl group is 6-membered. In some embodiments, the heteroaryl group is 9- or 10-membered bicyclic. In some embodiments, the heteroaryl is 9-member bicyclic. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. The nitrogen atoms in the ring(s) of the heteroaryl group can be oxidized to form N-oxides. Example heteroaryl groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, furanyl, thiophenyl, triazolyl, tetrazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzothiopheneyl, benzofuranyl, benzisoxazolyl, benzoimidazolyl, imidazo[1, 2-b]thiazolyl, purinyl, triazinyl, and the like. In some embodiments, the heteroaryl group is 9H-carbazol-2-yl; 1H-benzo[d]imidazol-6-yl; 1H-indol-6-yl; 1H-indazol-6-yl; 2H-indazol-4-yl; 1H-benzo[d][1,2,3]triazol-6-yl; benzo[d]oxazol-2-yl; quinolin-6-yl; or benzo[d]thiazol-2-yl.

Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthyridine, indole, benzofuran, purine, deazapurine, indolizine.

The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (e.g., the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl,

sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[d][1,3]dioxole-5-yl).

As used herein, the phrase "optionally substituted" means unsubstituted or substituted. As used herein, the term “substituted” or “substituted with one or more”, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). “Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

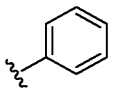
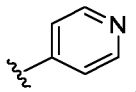
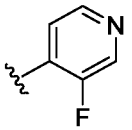
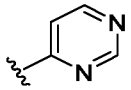
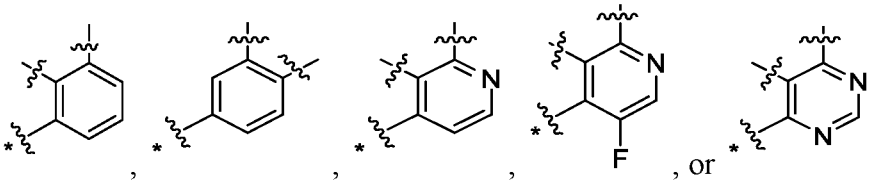
When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

As used herein, the term "heterocyclyl" or “heterocycloalkyl” employed alone or in combination with other terms, refers to a non-aromatic heterocyclic ring system, which may optionally contain one or more unsaturations as part of the ring structure, and which has at least one heteroatom ring member independently selected from nitrogen, sulfur, phosphorus, and oxygen. In some embodiments, the heterocyclyl group has 1, 2, 3, or 4 heteroatom ring members. In some embodiments, the heterocyclyl group has 1, 2, or 3 heteroatom ring members. In some embodiments, the heterocyclyl group has 1 or 2 heteroatom ring members. In some embodiments, the heterocyclyl group has 1 heteroatom ring member. When the

heterocyclyl group contains more than one heteroatom in the ring, the heteroatoms may be the same or different. Example ring-forming members include CH, CH_2, C(O), N, NH, O, S, S(O), and $S(=O)_2$. Heterocyclyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems. Polycyclic rings can include both fused systems and spirocycles. Also included in the definition of heterocyclyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the non-aromatic ring, for example, 1, 2, 3, 4-tetrahydro-quinoline, dihydrobenzofuran and the like. A heterocyclyl group that includes a fused aromatic moiety can be attached to the molecule through an atom from either the aromatic or non-aromatic portion. The carbon atoms or heteroatoms in the ring(s) of the heterocyclyl group can be oxidized to form a carbonyl, sulfinyl, or sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, heterocyclyl is 5- to 10-membered, 4- to 10-membered, 4- to 7-membered, 5-membered, or 6-membered. Examples of heterocyclyl groups include 1, 2, 3, 4-tetrahydro-quinolinyl, dihydrobenzofuranyl, azetidinyl, azepanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, and pyranyl. Examples of heterocyclyl groups that include one or more fused aromatic groups (*e.g.*, aryl or heteroaryl) include N-(2'-oxospiro[cyclohexane-1,3'-indolin]-6'-yl; 1,2,3,4-tetrahydroisoquinolin-6-yl; 2,3-dihydro-1H-benzo[d]imidazol-5-yl; 1,3-dihydrospiro[indene-2,3'-indolin]-6'-yl; 2,3-dihydrobenzo[d]oxazol-5-yl; 1,2-dihydroquinolin-7-yl; indolin-6-yl; spiro[cyclopentane-1,3'-indolin]-6'-yl; spiro[cyclohexane-1,3'-indolin]-6'-yl; chroman-6-yl; 3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl; and benzo[d][1,3]dioxol-5-yl.

As used herein, "" represents a bond to the position indicated by the corresponding variable, for example Ring A, R^1, R^2, R^3, Z, X^3, R^{3a}, R^{4a}, R^{4b}, $R^{4a'}$, or $R^{4b'}$.

As used in the embodiments describing Ring A, when Ring A is , , , or , it is intended that the position of the substituents can be at any position allowed by the available valences according to general formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, or a stereoisomer, or pharmaceutically acceptable salt thereof, e.g. ;

wherein * indicates attachment to Z.

As used herein, the term "isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture."

As used herein, the term "chiral center" refers to a carbon atom bonded to four nonidentical substituents.

As used herein, the term "chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al., Angew. Chem. Inter. Edit. 1966, 5, 385; errata 511; Cahn et al., Angew. Chem. 1966, 78, 413; Cahn and Ingold, J. Chem. Soc. 1951 (London), 612; Cahn et al., Experientia 1956, 12, 81; Cahn, J. Chem. Educ. 1964, 41, 116).

As used herein, the term "geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

As used herein, the term “atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

As used herein, the term “tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerisation is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerisations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R and S sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarised light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-) isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal

proportions of the enantiomers is called a "racemic mixture". The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereoisomers, are intended unless otherwise indicated. Where a compound name or structure is silent with respect to the stereochemistry of a stereocenter, all possible configurations at the stereocenter are intended. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

When the compounds of the disclosure contain a chiral center, the compounds can be any of the possible stereoisomers. In compounds with a single chiral center, the stereochemistry of the chiral center can be (R) or (S). In compounds with two chiral centers, the stereochemistry of the chiral centers can each be independently (R) or (S) so the configuration of the chiral centers can be (R) and (R), (R) and (S); (S) and (R), or (S) and (S). In compounds with three chiral centers, the stereochemistry each of the three chiral centers can each be independently (R) or (S) so the configuration of the chiral centers can be (R), (R) and (R); (R), (R) and (S); (R), (S) and (R); (R), (S) and (S); (S), (R) and (R); (S), (R) and (S); (S), (S) and (R); or (S), (S) and (S).

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereoisomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1, 2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

As used herein, the terms "E1" and "E2" correspond to first and second enantiomers to elute from a chiral chromatography column as discussed in the Examples.

When a disclosed compound is named or depicted without indicating the stereochemistry of one or more stereocenters, each of the stereoisomers resulting from the possible stereochemistries at the undefined stereocenter(s) are intended to be encompassed. For example, if a stereocenter is not designated as R or S, then either or both are intended.

Compounds of the disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1, 2, 4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the disclosure can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. Isotopes of constituent atoms of the compounds of the disclosure can be present in natural or non-natural abundance. Examples of isotopes of hydrogen include deuterium and tritium. In some embodiments, the compounds of the disclosure are deuterated, meaning at least one deuterium atom is present in the place of a hydrogen atom. In some embodiments, 1, 2, 3, 4, 5, 6, 7, or 8 hydrogens in a compound of the disclosure are replaced by deuterium. Methods for replacing hydrogen with deuterium in a molecule are known in the art.

The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified (*e.g.*, in the case of purine rings, unless otherwise indicated, when the compound name or structure has the 9H tautomer, it is understood that the 7H tautomer is also encompassed).

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be isolated.

It will be understood that the compounds of the present disclosure and any pharmaceutically acceptable salts thereof, comprise stereoisomers, mixtures of stereoisomers, polymorphs of all isomeric forms of said compounds.

In some embodiments, the compounds of the disclosure, or salts thereof, or crystalline forms of any of the aforementioned, are purified or substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in a compound of the disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the disclosure, or salt thereof. In some embodiments, the compounds of the disclosure, or salts thereof, or crystalline forms of any of the aforementioned, can be prepared with a purity of about 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more.

The phrase "pharmaceutically acceptable" is employed herein to refer to 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 problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" or "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of

the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol, or butanol) or acetonitrile (MeCN) are preferred.

The compounds disclosed herein include the compounds themselves, as well as their salts, their solvates, and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., protonated amino) on a compound of this disclosure. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluroacetate). The term "pharmaceutically acceptable anion" refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a compound of this disclosure. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The compounds of this disclosure also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active compounds of this disclosure.

Additionally, physiologically acceptable, i.e., pharmaceutically compatible, salts can be salts of the compounds disclosed herein with inorganic or organic acids. Preference is given to salts with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or to salts with organic carboxylic or sulphonic acids, such as, for example, acetic acid, trifluoroacetic acid, propionic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

Other pharmaceutically compatible salts which may be mentioned are salts with customary bases, such as, for example, alkali metal salts (for example sodium or potassium salts), alkaline earth metal salts (for example calcium or magnesium salts) or ammonium salts, derived from ammonia or organic amines, such as, for example, diethylamine, triethylamine,

ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine or methylpiperidine.

As used herein, "pharmaceutically acceptable salts" can refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, e.g., glycine, alanine, phenylalanine, arginine, etc.

Other examples of pharmaceutically acceptable salts can include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, or an alkaline earth metal ion, e.g., an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, diethylamine, diethylaminoethanol, ethylenediamine, imidazole, lysine, arginine, morpholine, 2-hydroxyethylmorpholine, dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine, tetramethylammonium hydroxide and the like.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

It is to be understood that, unless otherwise stated, any description of a method of treatment or prevention includes use of the compounds to provide such treatment or prevention as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment or prevention includes use of the compounds to prepare a medicament to treat or prevent such condition. The treatment or prevention includes treatment or prevention of human or non-human animals including rodents and other disease models.

It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment includes use of the compounds to prepare a medicament to treat such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

As used herein, the term "subject" includes human and non-human animals, as well as cell lines, cell cultures, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

As used herein, the term "subject in need thereof" refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

As used herein, the term "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease,

condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model. It is to be appreciated that references to "treating" or "treatment" include the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

It is to be understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

As used herein, the term "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al., Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

The compounds of the present disclosure may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure

contains a suitable group or substituent to which a property-modifying group can be attached. Examples of prodrugs include derivatives containing in vivo cleavable alkyl or acyl substituents at the sulfonylurea group in a compound of the any one of the Formulae disclosed herein.

Accordingly, the present disclosure includes those compounds of the present disclosure as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the present disclosure includes those compounds of the present disclosure that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the present disclosure may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the following documents: a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985); c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 “Design and Application of Pro-drugs”, by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984); g) T. Higuchi and V. Stella, “Pro-Drugs as Novel Delivery Systems”, A.C.S. Symposium Series, Volume 14; and h) E. Roche (editor), “Bioreversible Carriers in Drug Design”, Pergamon Press, 1987.

A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses a hydroxy group is, for example, an in vivo cleavable ester or ether thereof. An in vivo cleavable ester or ether of a compound of the present disclosure containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C1-C10 alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C1-C10 alkoxycarbonyl groups such as ethoxycarbonyl, N,N-(C1-C6

alkyl)2carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C1-C4 alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses a carboxy group is, for example, an in vivo cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C_1-C_4 alkylamine such as methylamine, a (C_1-C_4 alkyl)$_2$amine such as dimethylamine, N-ethyl N-methylamine or diethylamine, a C1-C4 alkoxy C2-C4 alkylamine such as 2 methoxyethylamine, a phenyl C_1-C_4 alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses an amino group is, for example, an in vivo cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C_1-C_{10} alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl, and 4-(C1-C4 alkyl)piperazin-1-ylmethyl.

The in vivo effects of a compound of the present disclosure may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the present disclosure. As stated hereinbefore, the in vivo effects of a compound of the present disclosure may also be exerted by way of metabolism of a precursor compound (a prodrug).

All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed

as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

As use herein, the phrase "compound of the disclosure" refers to those compounds which are disclosed herein, both generically and specifically.

Synthesis

In some aspects, the present disclosure provides a method of preparing a compound disclosed herein.

In some aspects, the present disclosure provides a method of preparing a compound, comprising one or more steps as described herein.

In some aspects, the present disclosure provides a compound obtainable by, or obtained by, or directly obtained by a method for preparing a compound described herein.

In some aspects, the present disclosure provides an intermediate being suitable for use in a method for preparing a compound described herein.

The compounds of the present disclosure can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilized.

It will be appreciated that during the synthesis of the compounds of the disclosure in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed. For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule. Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl (Bn). The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively, an acyl group such as a tert butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or

ammonia. Alternatively, an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

Once a compound of the present disclosure has been synthesized by any one of the processes defined herein, the processes may then further comprise the additional steps of: (i) removing any protecting groups present; (ii) converting the compound of the present disclosure into another compound of the present disclosure; (iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or (iv) forming a prodrug thereof.

The resultant compounds of the present disclosure can be isolated and purified using techniques well known in the art.

Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, cyclopentylmethyl ether (CPME), methyl tert-butyl ether (MTBE) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone, methylisobutylketone (MIBK) or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methylpyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate or methyl acetate, or mixtures of the said solvents or mixtures with water.

The reaction temperature is suitably between about -100 °C and 300 °C, depending on the reaction step and the conditions used.

Reaction times are generally in the range between a fraction of a minute and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for

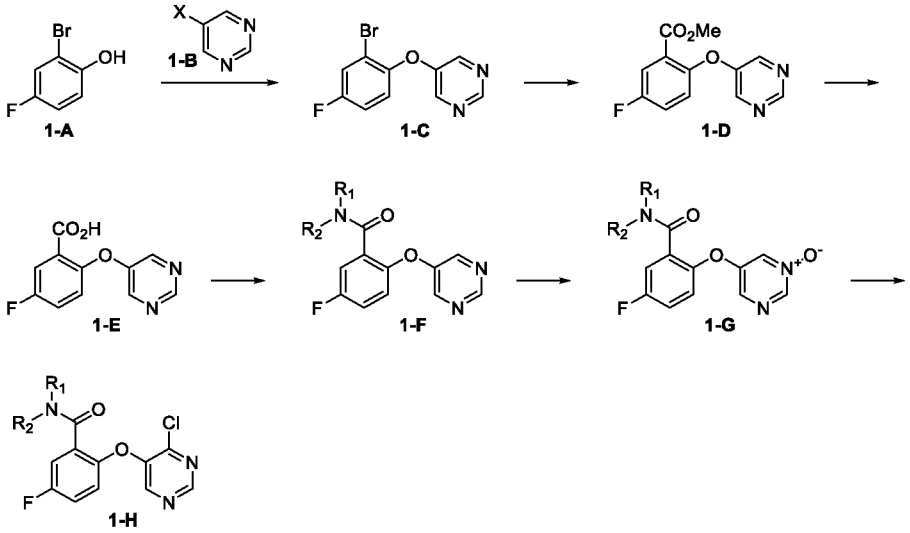
example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range between 10 minutes and 48 hours.

Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present disclosure can be readily prepared. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

As will be understood by the person skilled in the art of organic synthesis, compounds of the present disclosure are readily accessible by various synthetic routes, some of which are exemplified in the accompanying examples. The skilled person will easily recognize which kind of reagents and reactions conditions are to be used and how they are to be applied and adapted in any particular instance – wherever necessary or useful – in order to obtain the compounds of the present disclosure. Furthermore, some of the compounds of the present disclosure can readily be synthesized by reacting other compounds of the present disclosure under suitable conditions, for instance, by converting one particular functional group being present in a compound of the present disclosure, or a suitable precursor molecule thereof, into another one by applying standard synthetic methods, like reduction, oxidation, addition or substitution reactions; those methods are well known to the skilled person. Likewise, the skilled person will apply – whenever necessary or useful – synthetic protecting (or protective) groups; suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, e.g., P.G.M. Wuts, T.W. Greene, "Greene's Protective Groups in Organic Synthesis", 4th edition (2006) (John Wiley & Sons).The compounds of the disclosure can be synthesized by the methods described in Schemes 1-8 below. The synthesis of various hydroxyl-substituted heterocycles is well documented in the literature and can be synthesized by known literature methods. The depicted intermediates may also be available as commercial reagents from numerous vendors.

The compounds of the present disclosure can be prepared according to the general methods illustrated in the following Schemes.

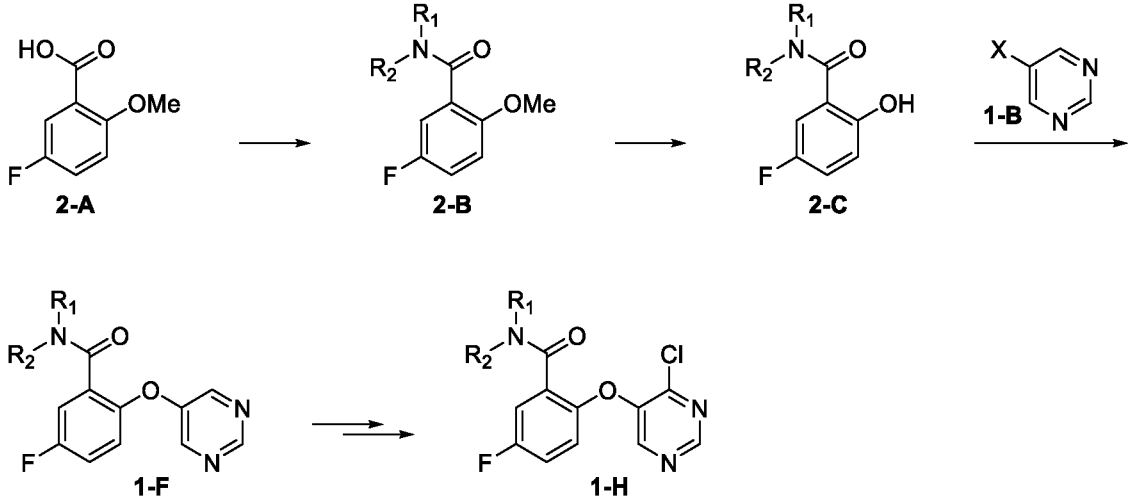
Scheme 1



Scheme 1 illustrates the general method for the preparation of key intermediates like compound **1-H**. A suitably substituted 2-halophenol, for instance 4-fluoro-2-bromophenol (**1-A**), is reacted with a 5-halopyrimidine (**1-B**), for example 5-bromopyrimidine or 5-iodopyrimidine, to afford the corresponding diaryl ether (**1-C**). This reaction is typically conducted in the presence of an acid scavenger like Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, Et_3N (triethylamine) or $(iPr)_2NEt$ (diispropylethylamine, also known as Hunig's base), in a suitable, neutral solvent, such as DMA (dimethyl acetamide) or NMP (*N*-methylpyrrolidinone). In some instances, this transformation can be facilitated by addition of an appropriate catalyst, typically Cu_2O or CuI, in the presence of a suitable ligand, for example *rel*-(1*R*,2*R*)-N^1,N^2-bis(2-pyridinylmethylene)-1,2-cyclohexanediamine or 3,4,7,8-tetramethyl-1,10-phenanthroline. Conversion of compound **1-C** to compound **1-D** can be readily achieved by carbonylation under Pd catalysis, in the presence of an acid scavenger and suitable alcohol (typically used as the solvent in the reaction). Oftentimes, $Pd(dppf)Cl_2$ (dppf = 1,1-bis(diphenylphosphino)ferrocene) is used as the palladium catalyst, but other catalyst systems, such as $Pd(Ph_3P)_2Cl_2$ (Ph_3P = triphenylphosphine) or $Pd(OAc)_2$ with Ph_3P, can also be used. Commonly, Et_3N or $(i\text{-}Pr)_2NEt$ are used as the acid scavengers, and methanol is used as the solvent. These reactions are most typically run under an atmosphere of CO, but other CO sources, for example oxalic acid, can be used in some instances. The ester group of compound **1-D** is subsequently saponified to the corresponding carboxylic acid **1-E**. Typically, this transformation is accomplished using LiOH, NaOH or KOH, in an aqueous solvent system, such as methanol/water or THF/water. The carboxylic acid is then converted to an amide (**1-F**). Many different conditions have been developed to achieve this type of transformation, and will be generally familiar to those of skill in the art. For instance, the carboxylic acid can be

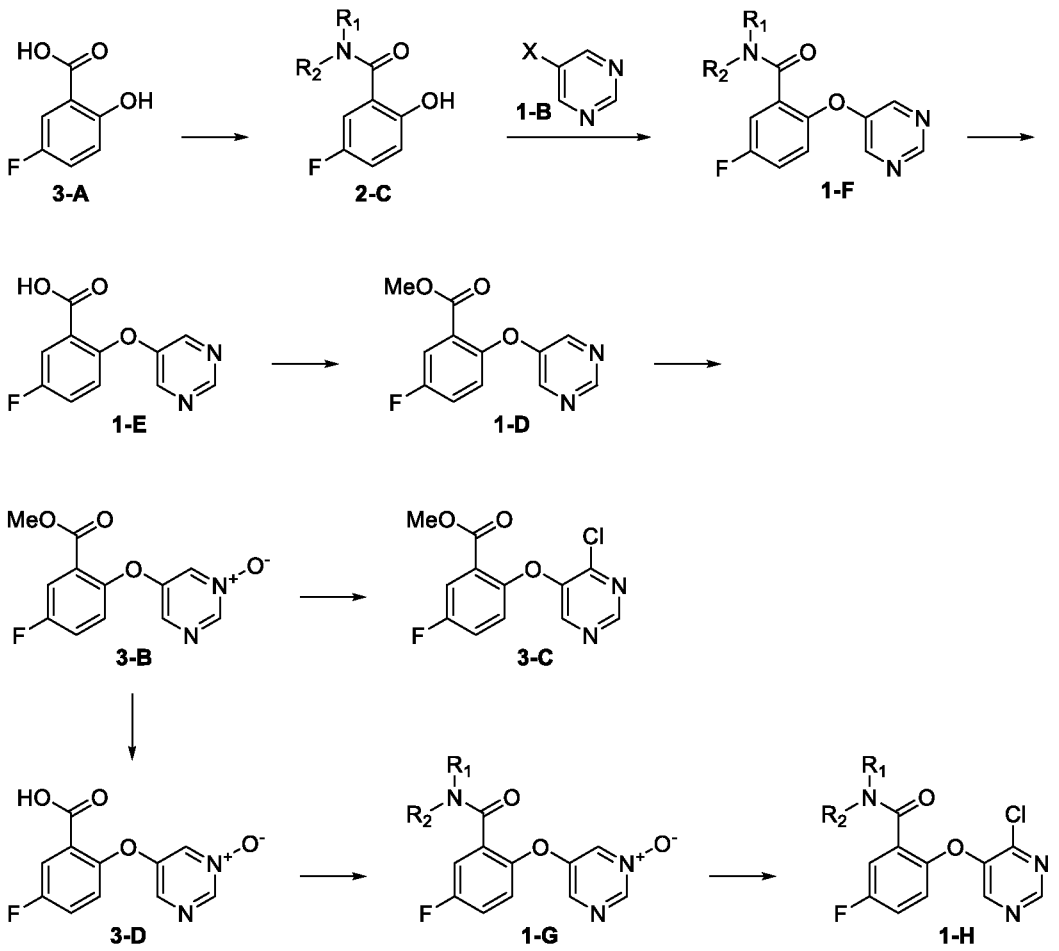
reacted with thionyl chloride or oxalyl chloride, which forms the corresponding acid chloride. This reaction can be conducted in a suitable, neutral solvent like CH_2Cl_2 or THF, or if thionyl chloride is used, can be run with thionyl chloride as the reactant and solvent, if desired. The acid chloride is subsequently reacted with a suitable amine, R_1R_2NH, in the presence of an appropriate acid scavenger, for example Et_3N, $(i\text{-}Pr)_2NEt$, or pyridine, in a neutral solvent like CH_2Cl_2 or THF. In some instances, pyridine can be used as the acid scavenger and the solvent for the reaction. Sometimes, a strong base like sodium hydride, in a neutral solvent like THF, DMF, or toluene, is used. Alternatively, the carboxylic acid and amine R_1R_2NH can be combined together and coupled using a reagent such as DCC (dicyclohexyl carbodiimide), EDC (1-ethyl-3-(4-dimethylaminopropyl)carbodiimide), HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), T3P, or $POCl_3$, in the presence of an appropriate acid scavenger, for example Et_3N, $(i\text{-}Pr)_2NEt$, or pyridine, in a neutral solvent, oftentimes DMF, NMP, CH_2Cl_2 or THF. In some instances, when DCC or EDC is used as the coupling reagent, HOBt (hydroxybenzotriazole) might be added to the reaction to facilitate the desired coupling reaction. Reaction of **1-F** with a suitable oxidizing agent, such as urea hydroperoxide in the presence of trifluoroacetic anhydride, or *meta*-chloroperoxybenzoic acid (mCPBA), in a suitable solvent, typically CH_2Cl_2 or THF, affords the pyrimidine *N*-oxide **1-G**. This then can be chlorinated to afford compound **1-H** using an appropriate chlorinating agent, typically $POCl_3$ or oxalyl chloride, in the presence of an acid scavenger, usually Et_3N, $(i\text{-}Pr)_2NEt$, in a neutral solvent like CH_2Cl_2, ethyl acetate (EtOAc), or isopropyl acetate.

Scheme 2



Scheme 2 illustrates an alternative method to prepare the key intermediate **1-H**. The benzoic acid derivative **2-A** is converted to the corresponding amide **2-B**, according to the general conditions for preparing amides from carboxylic acids described in Scheme 1 (see **1-E** to **1-F**). The methyl ether protecting group in **2-B** can then be removed in a variety of ways as described in Greene's Protective Groups in Organic Synthesis, 4th Edition (ISBN:9780470053485). For example, reaction of **2-B** with boron tribromide (BBr_3), in a neutral solvent, typically CH_2Cl_2, provides phenol **2-C**. This phenol can be reacted with a 5-halopyrimidine (**1-B**), as described in Scheme 1 (see **1-A** to **1-C**), to afford the diaryl ether **1-F**. This compound can then be transformed into the key intermediate **1-H** as described in Scheme 1.

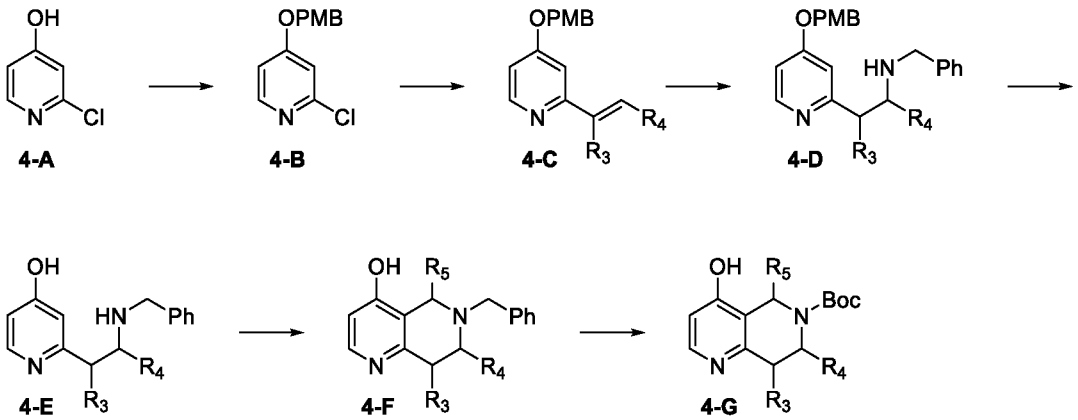
Scheme 3



Scheme 3 illustrates the general methods for preparing the key intermediate **3-C**, as well as an alternative method to prepare compound **1-H**. The carboxylic acid **3-A** can be converted to the amide **2-C** according to the general methods described in Scheme 2. Preferably, however, carboxylic acid **3-A** is first converted to an intermediate acid chloride (not shown), using thionyl chloride, in a neutral solvent like CH_2Cl_2 or THF, and that acid

chloride is then reacted with a suitable amine to afford amide **2-C**. Typically, *N*,*N*-dimethylamine is the amine of choice for this particular chemistry, which affords the *N*,*N*-dimethyl amide (**2-C**; R_1 and R_2 = CH_3). Amide **2-C** is then reacted with a 5-halopyrimidine (**1-B**), for example 5-bromopyrimidine or 5-iodopyrimidine, as generally described in Scheme 1, to afford the corresponding diaryl ether **1-F**. The amide group of compound **1-F** is subsequently saponified to the corresponding carboxylic acid **1-E**. Typically, this transformation is accomplished using LiOH, NaOH or KOH, in an aqueous solvent system, such as methanol/water or THF/water. Heat can be used to increase the reaction rate. The carboxylic acid is then converted to ester **1-D**. The transformation of a carboxylic acid to an ester is usually achieved by reacting the carboxylic acid with an alcohol, such as methanol of ethanol, in the presence of an acid catalyst like HCl or H_2SO_4. Typically, the alcohol is used as the solvent, and heat can be used to increase the reaction rate. Alternatively, **1-E** can be O-alkylated using methyl iodide in the presence of an acid scavenger, oftentimes K_2CO_3, to afford **1-E**. Note that an alternative preparation of **1-D** was described in Scheme 1. Reaction of **1-D** under oxidizing conditions, such as those described in Scheme 1, delivers the *N*-oxide derivative **3-B**, which can be chlorinated, according to the general conditions described in Scheme 1, to afford the key intermediate **3-C**. It will be appreciated by those of skill in the art that compound **3-C** is a flexible intermediate that can be converted into the compounds of the present invention in a variety of ways. Alternatively, if desired, compound **3-B** can be saponified to the corresponding carboxylic acid **3-D**, according to the general saponification conditions described above. Carboxylic acid **3-D** can be subsequently converted to the corresponding amide **1-G** according to the general methods for amide formation described previously. Compound **1-G** can, in turn, be converted to compound **1-H** as described in Scheme 1.

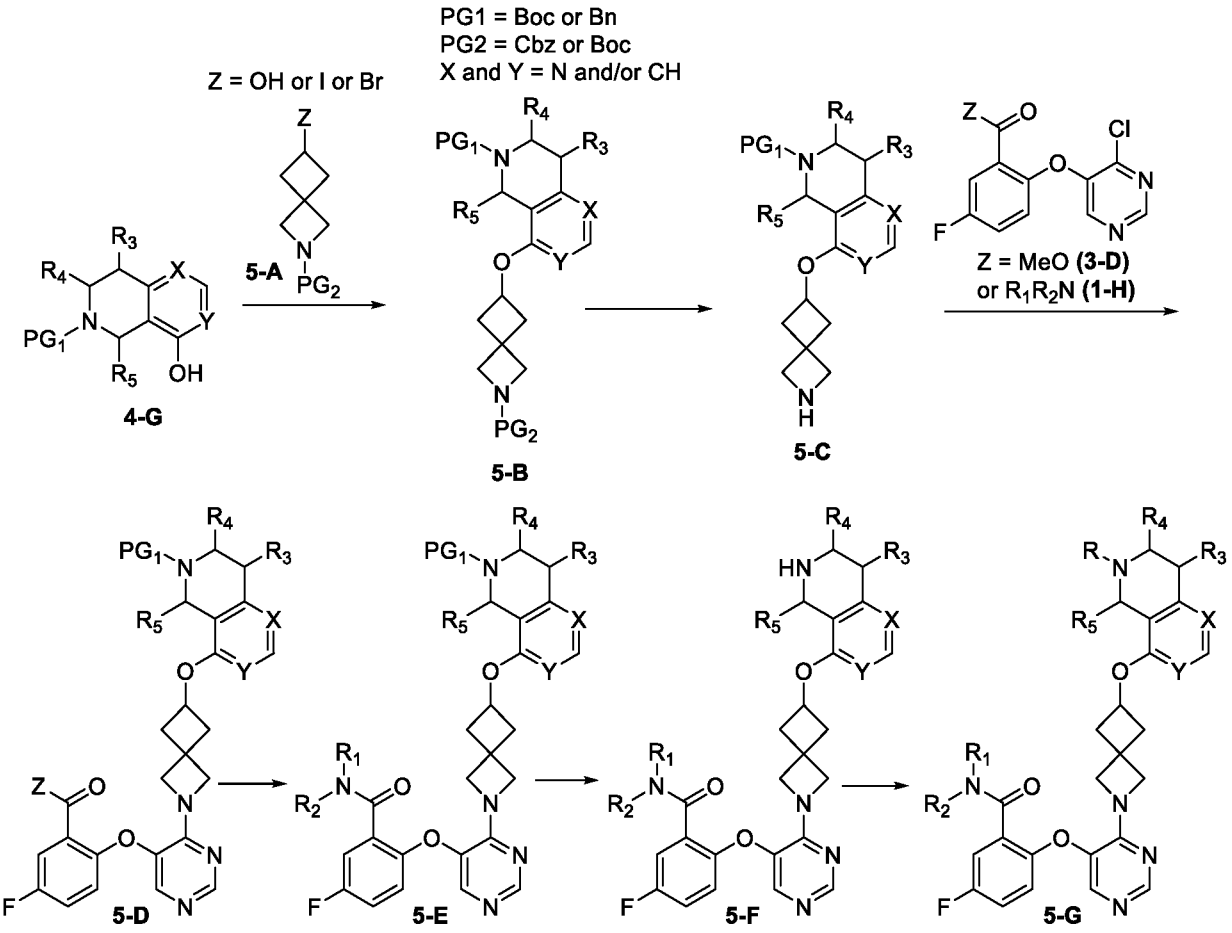
Scheme 4



Scheme 4 illustrates the general method for the preparation of key intermediates like compound **4-G**. A suitable 2-halo-4-hydroxypyridine, for instance 2-chloro-4-hydroxypyridine (**4-A**), is reacted with an appropriate alkylating or acylating agent, for instance 4-methoxybenzyl chloride, to afford the protected derivative **4-B**. The protecting group is selected so that it can be removed selectively when desired. Note that, in some instances, the protecting group might attach to nitrogen, to afford an *N*-substituted 4-pyridone derivative (not shown). This would be considered acceptable, as long as the position of the protecting group (O vs. N) does not interfere with the ensuing chemistry. Compound **4-B** is subsequently transformed to compound **4-C**. Typically, this transformation is accomplished by reacting **4-B** with a suitable olefinic boron reagent, for instance potassium vinyltrifluoroborate, vinylboronic acid, vinylboronic acid pinacol ester (also known as 2-vinyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane), isopropenylboronic acid, isopropenylboronic acid pinacol ester (also known as 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane), propenylboronic acid, or propenylboronic acid pinacol ester (also known as 4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane). The corresponding olefinic stannanes, for instance tributylvinyltin (also known as tributyl(vinyl)stannane), might also be used. This reaction is typically mediated by a palladium catalyst, such as $PdCl_2$; $Pd(OAc)_2$, or $[(Ph3P)]_4Pd$, oftentimes in the presence of a ligand for Pd, such as dibenzylideneacetone or 1,1'-bis(diphenylphosphino)ferrocene (dppf). Typically, an acid scavenger, like Et_3N, Hunig's base, potassium carbonate, or cesium carbonate, is used, and the reaction is conducted in an appropriate solvent, such as ethanol, tetrahydrofuran, or 1,4-dioxane. As an example of this type of reaction, compound **4-B** can be reacted with potassium vinyltrifluoroborate, $PdCl_2$(dppf), and Et_3N in ethanol to afford **4-C** ($R_3 = R_4 = H$). Reaction of **4-C** with an appropriate amine, for instance benzylamine, produces **4-D**. This reaction oftentimes requires an acidic catalyst, such as acetic acid, in methanol or ethanol as the solvent. Removal of the protecting group then delivers **4-E.** As indicated previously, conditions for adding and removing protecting groups are described in established reference volumes, for instance Greene's Protective Groups in Organic Synthesis, 4th Edition (ISBN:9780470053485). In the case of **4-E**, the 4-methoxybenzyl group can be selectively removed using trifluoroacetic acid (TFA) in a neutral solvent like CH_2Cl_2 or 1,2-dichloroethane. Compound **4-E** will react with aldehydes in a classic Pictet-Spengler-type reaction. Typical solvents for this type of reaction include methanol, ethanol, n-butanol, or DMSO, and sometimes, a base like Et_3N, Hunig's base, or K_2CO_3 is used. For example, reaction of **4-E** with formalin in methanol or ethanol affords the tetrahydronaphthyridine derivative **4-F**. Reaction with other aldehydes, for instance acetaldehyde, would deliver **4-F**

(R_5 = CH_3). If desired, the benzyl group on the basic nitrogen of **4-F** can be removed by hydrogenolysis over a palladium catalyst, typically using hydrogen gas in the presence of a palladium catalyst (oftentimes palladium on activated carbon). This reaction is typically conducted in a solvent like acetic acid, methanol, ethanol, ethyl acetate, or mixtures thereof. Sometimes, a strong acid (like HCl) is incorporated into the reaction to afford the acid salt of the amine. Alternatively, if this reaction is conducted in the presence of Boc anhydride, in a solvent like methanol, ethanol, ethyl acetate, or mixtures thereof, the *N*-Boc derivative **4-G** would emerge from the reaction. Compounds **4-F** and **4-G** are both useful intermediates for preparing the compounds of this invention.

Scheme 5



Scheme 5 illustrates the general methods for converting the key intermediate **4-G** into the compounds of the present invention (**5-F** and **5-G**) (X and Y = N and/or CH). Compound **4-G** (X = N, Y = CH), which can be prepared according to the general procedures described in Scheme 4, can be reacted with an appropriate aliphatic iodo/bromo compound **5-A**, under standard O-alkylation conditions, to afford compound **5-B**. The O-alkylation reaction can be performed under a wide range of conditions well-known to those of skill in the art. For example,

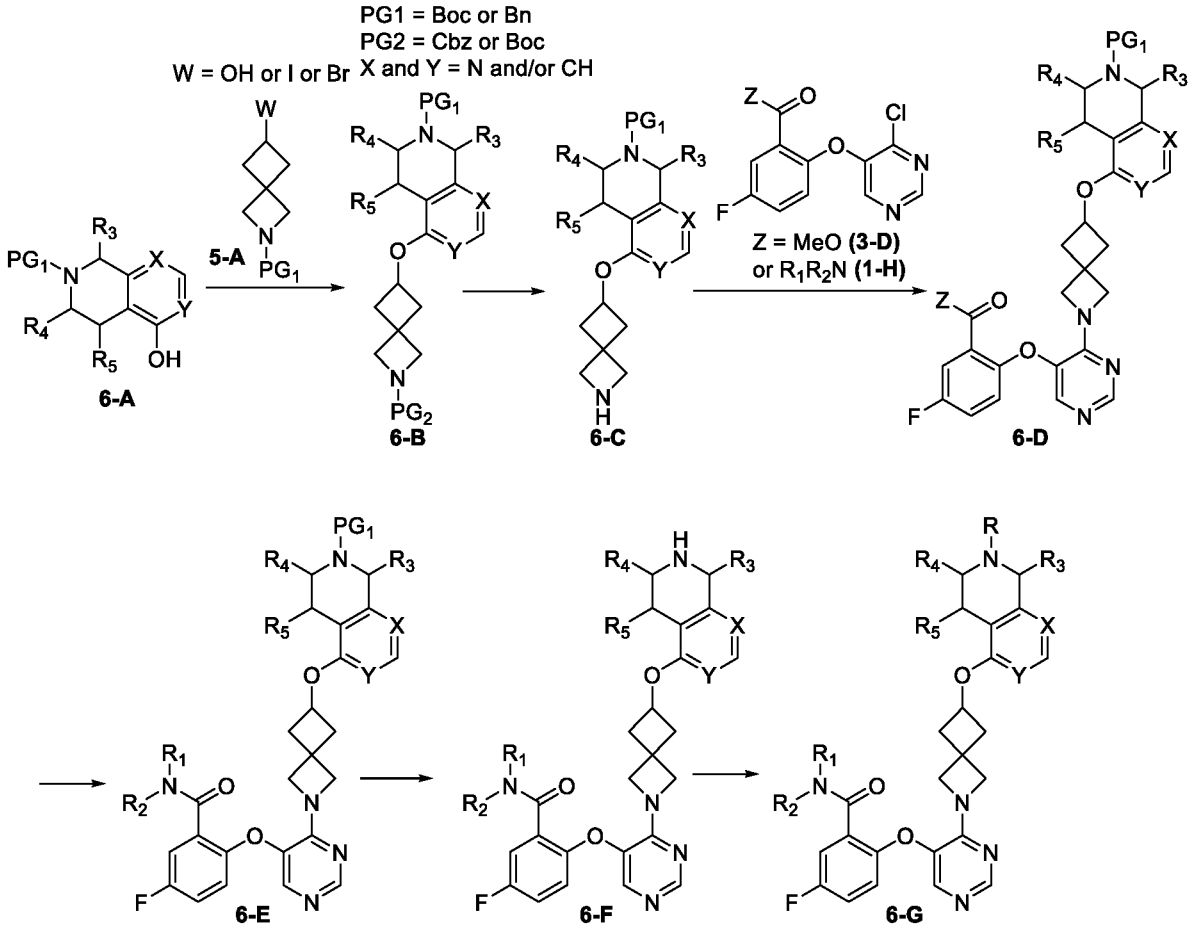
compound **4-G** and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate can be combined in the presence of a base, such as Na_2CO_3, K_2CO_3, or Cs_2CO_3, in a neutral solvent like THF, DMF, DMSO or NMP, at elevated temperature, to afford **5-B**. Alternatively, **5-B** can be synthesized using **4-G** and an appropriate alcohol, for instance, a suitably protected variant of 2-azaspiro[3.3]heptan-6-ol, under Mitsunobu conditions. Typically, a Mitsunobu reaction is conducted using a diazodicarboxylate, typically DEAD (diethyl azodicarboxylate), DIAD (diisopropyl azodicarboxylate), or ADDP (1,1'-(azodicarbonyl)dipiperidine), and an appropriate phosphine, typically PPh_3 (triphenylphosphine). Alternatively, the coupling can be mediated by the Tsunoda reagent (2-tributylphosphoranylidene)acetonitrile). The reaction is conducted in a neutral solvent like THF, ACN, CH_2Cl_2 or toluene. On the other hand, one might employ a copper (II) catalyzed coupling reaction to prepare **5-B**, using an appropriate boron reagent like a potassium aryltrifluoroborate, and a suitably protected variant of 2-azaspiro[3.3]heptan-6-ol. This type of reaction is usually conducted in the presence of a ligand like TMEDA or 1,10-phenanthroline, in the presence of a base like pyridine or DMAP, in a neutral solvent like CH_2Cl_2. Another approach to prepare compound **5-B** could be to react compound **4-G** (where, X and Y = N, Cl instead of OH) with an appropriate alcohol **5-A**, using a strong base like KOtBu or sodium hydride, in a neutral solvent like THF, DMF, DMSO or NMP. As an example of this type of reaction, compound **4-G** (where X and Y = N; Cl instead of OH) can be reacted with benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate and sodium hydride in DMF to afford **5-B** (where X and Y = N) at RT. Removal of the protecting group then affords compound **5-C**, which is a useful intermediate that can be used to make additional compounds. The use of protecting groups in organic synthesis is well-known to those of skill in the art, and conditions for adding and removing protecting groups are described in established reference volumes, for instance, Greene's Protective Groups in Organic Synthesis, 4th Edition (ISBN:9780470053485). For instance, when the protecting group PG2 in **5-B** is Cbz, deprotection is oftentimes achieved under hydrogenolysis conditions, to give compound **5-C**. Hydrogenolysis is accomplished by reaction with hydrogen gas, generally in the presence of a palladium catalyst, such as palladium on activated carbon (Pd/C) or $Pd(OH)_2$. Sometimes, AcOH or HCl is added to the reaction mixture, and a suitable solvent, like methanol, ethanol, 2,2,2-trifluoroethanol, ethyl acetate, or a combination thereof, is typically used. Sometimes, PtO_2 can be used as a hydrogenolysis catalyst. When the protecting group PG2 in **5-B** is Boc (*tert*-butyloxycarbonyl), deprotection is oftentimes accomplished under acidic conditions, using acids like HCl, TFA (trifluoracetic acid), or *p*-TsOH (*para*-toluenesulfonic acid), in a

suitable solvent, oftentimes CH_2Cl_2, THF or 1,4-dioxane. Preferably, the Boc group in compound **5-B** is removed with TMSCl in 2,2,2-trifluoroethanol.

The amine compound **5-C** can be readily reacted with the chloride of compound **3-D** (Z = MeO) or compound **1-H** (Z = R_1R_2N). This reaction is conducted in the presence of an acid scavenger, usually Et_3N or $(i\text{-}Pr)_2NEt$, in a solvent like IPA, *t*-BuOH, n-BuOH, *tert*-amyl alcohol, CH_2Cl_2, THF, DMF, or isopropyl acetate. When Z = OMe, the ester group is subsequently saponified to the corresponding carboxylic acid (not shown in the scheme). Typically, this transformation is accomplished using LiOH, NaOH or KOH, in an aqueous solvent system, such as methanol/water or THF/water. If desired, the carboxylic acid can also be isolated as the Li, Na, or K salt. The carboxylic acid is then converted to an amide (**5-E**). Many different conditions have been developed to achieve this type of transformation and will be generally familiar to those of skill in the art. For instance, the carboxylic acid can be reacted with thionyl chloride or oxalyl chloride, which forms the corresponding acid chloride. This reaction can be conducted in a suitable, neutral solvent like CH_2Cl_2, or if thionyl chloride is used, can be run with thionyl chloride as the reactant and solvent. The acid chloride is subsequently reacted with a suitable amine, R1R2NH, in the presence of an appropriate acid scavenger, for example, Et_3N, $(i\text{-}Pr)_2NEt$, or pyridine, in a neutral solvent like CH_2Cl_2 or THF. In some instances, pyridine can be used as the acid scavenger and the solvent for the reaction. Alternatively, the carboxylic acid and amine R1R2NH can be combined and coupled using a reagent such as DCC (dicyclohexyl carbodiimide), EDC (1-ethyl-3-(4-dimethylaminopropyl)carbodiimide), HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), or T3P, in the presence of an appropriate acid scavenger, for example, Et_3N, $(i\text{-}Pr)_2NEt$, or pyridine, in a neutral solvent, oftentimes DMF, NMP, CH_2Cl_2 or THF. In some instances, when DCC or EDC is used as the coupling reagent, HOBt (hydroxybenzotriazole) might be added to the reaction to facilitate the desired coupling reaction. When Z = R1R2N, reaction with **5-C** affords **5-E** directly. When a protecting group (PG1) is required, it can be removed subsequently according to the nature of the protecting group. For instance, when the protecting group PG1 in **5-E** is Boc, deprotection is achieved according to the general methods described for the Boc-deprotection under acidic condition (see **5-B** to **5-C**), to give compound **5-F**. This can be isolated as a salt, where n HX denotes the salt form, or as the free base, following work-up under standard basic conditions. When PG1 = Bn in **5-E**, deprotection can be accomplished according to the general methods described for the Cbz-deprotection under hydrogenolysis conditions (see **5-B** to **5-C**).

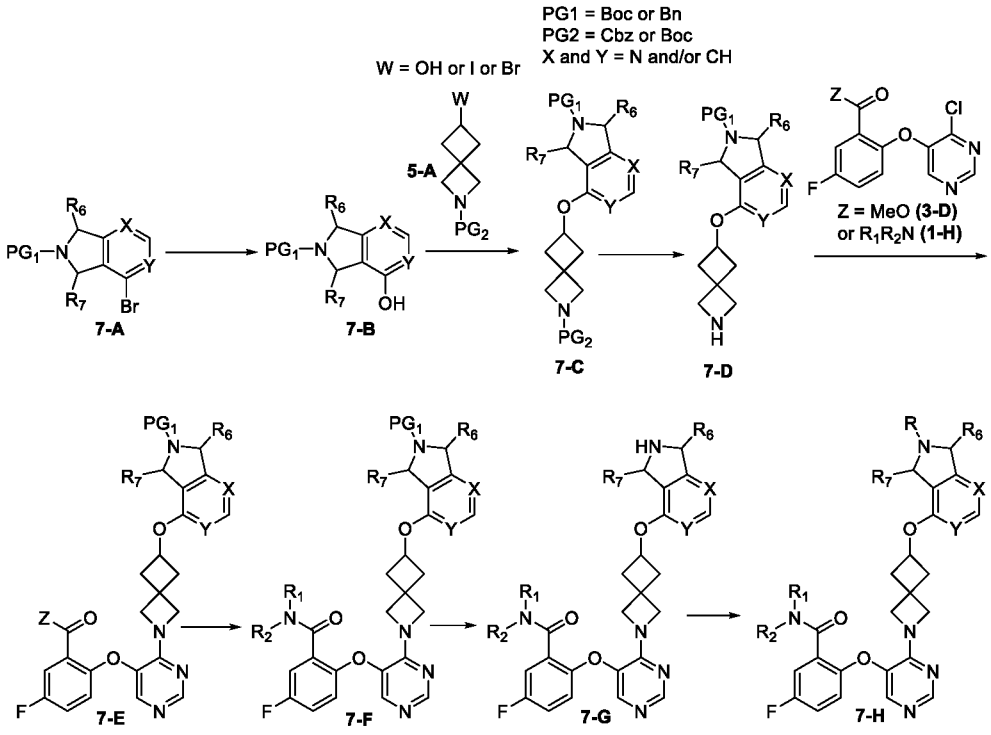
If desired, **5-F** can be *N*-alkylated to afford compound **5-G** (X and Y = N and/or CH, R = an appropriate alkyl group). In this type of reaction, **5-F** reacts with an alkyl halide, alkyl OTf, or alkyl OTs to afford the alkylated product **5-G**. This reaction can be conducted in the presence of a base like, Na_2CO_3, K_2CO_3, Cs_2CO_3, Et_3N (triethylamine) or $(iPr)_2NEt$ (diispropylethylamine, also known as Hunig's base), in a suitable, neutral solvent, such as ACN, THF, DMF, DMA (dimethyl acetamide) or NMP (*N*-methylpyrrolidinone). Alternatively, **5-F** can react with a suitable aldehyde or ketone in a reductive amination reaction. This reaction can be conducted in the presence of STAB (sodium triacetoxyborohydride) or $NaCNBH_3$ (sodium cynoborohydride) and acetic acid, in a suitable solvent, such as MeOH, DCE, CH_2Cl_2, THF, DMF or NMP or a combination thereof. In a representative example, formaldehyde can be reacted with **5-F** in the presence of STAB (sodium triacetoxyborohydride) and AcOH, in DCE to afford the *N*-methylated compound **5-G**. Alternatively, another approach to convert compound **5-F** to **5-G** is to react **5-F** with a dihaloalkane (like 1-bromo-3-chloropropane) in the presence of Na_2CO_3, K_2CO_3, Cs_2CO_3, Et_3N or $(iPr)_2NEt$, in a suitable, neutral solvent, such as ACN, THF, DMF or DMA to obtain the corresponding, *N*-alkylated halo intermediate (not shown in the scheme). This can further react with R_1R_2NH, in the presence of a base, such as Et_3N or $(iPr)_2NEt$), in a suitable, neutral solvent, such as ACN, THF or DMF, to afford compound **5-G**.

Scheme 6



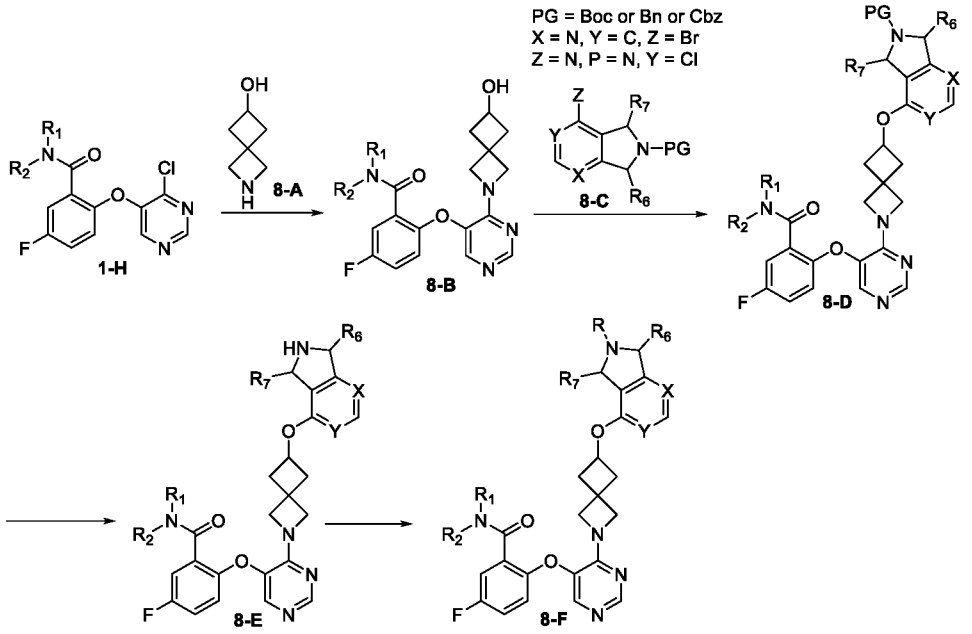
Scheme 6 illustrates the general methods for converting compound **7-A** into the compounds of the present invention **(6-F** and **6-G)** (X and Y = N and/or CH)**.** O-Alkylation of **6-A** using **5-A** can be accomplished using the general procedures described in Scheme 5 (see **4-G** to **5-B**). Removal of the protecting group (PG2 = Cbz or Boc) of **6-B** can be accomplished using the general procedures for removing Cbz or Boc group as described in Scheme 5 (see **5-B** to **5-C**) to afford **6-C**. This can be converted to the compound **(6-E)** as described in Scheme 5 (see **5-C** to **5-E**). Removal of the protecting group (PG1 = Boc or Bn) of **6-E** affords **6-F (**see **5-B** to **5-C)**. Subsequently, if desired, *N*-alkylation with a suitable alkylating agent, according to the general methods described in Scheme 5 (see **5-F** to **5-G**), affords **6-G**. The resulting amines **6-F** and **6-G** can be isolated as the free base or as a suitable salt form, as discussed in Scheme 5.

Scheme 7



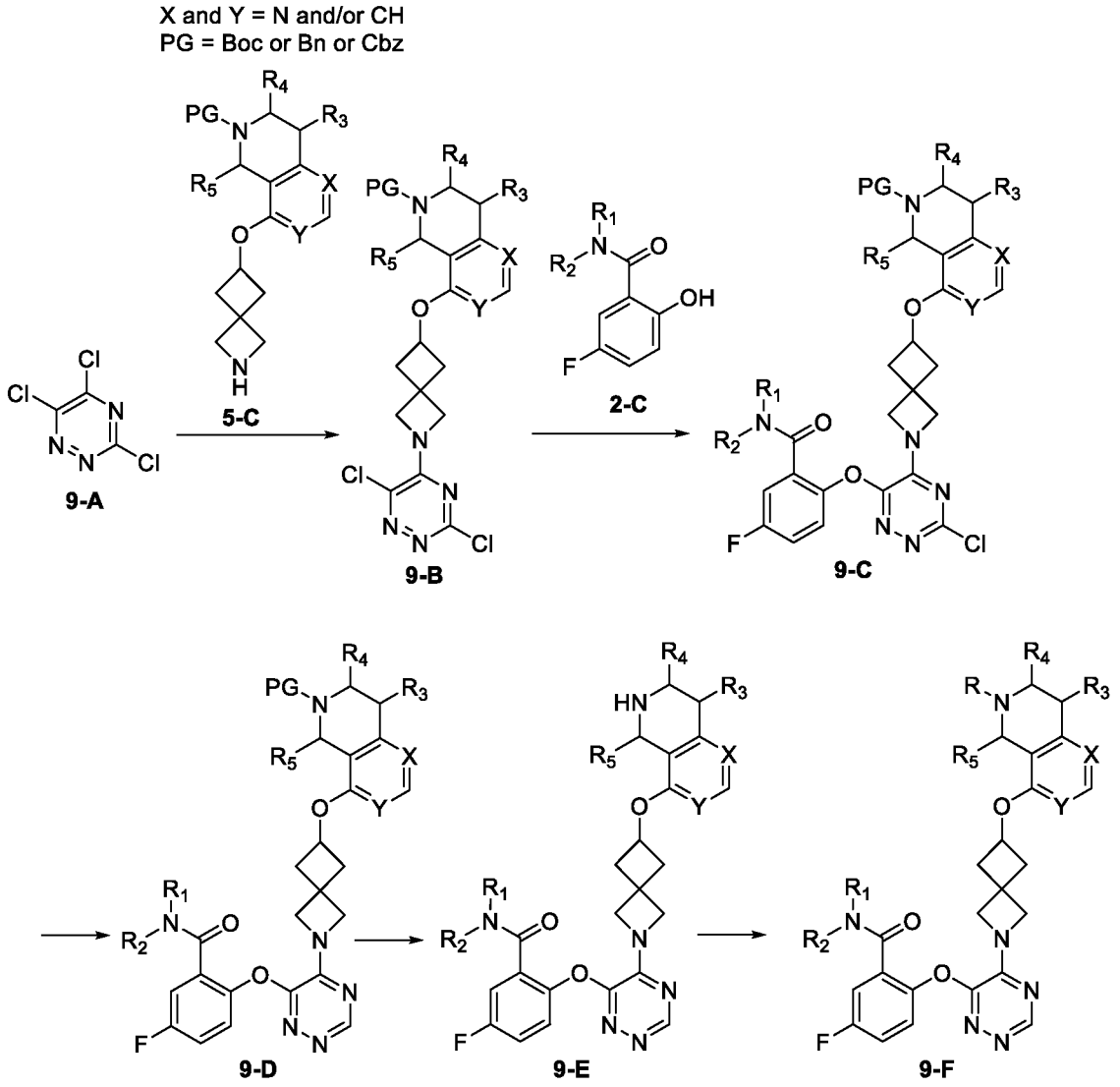
Scheme 7 illustrates the general methods for converting compound **7-A** into the compounds of the present invention **(7-G** and **7-H)** (X and Y = N and/or CH)**.** Hydroxylation of **7-A** can be accomplished using KOH or NaOH in the presence of Pd catalyst, such as $PdCl_2$; $Pd(OAc)_2$, or $[(Ph_3P)]_4Pd$, oftentimes in the presence of a ligand for Pd, such as dibenzylideneacetone or 1,1'-bis(diphenylphosphino)ferrocene (dppf). Solvents for this type of reaction typically include THF, DMSO, or toluene with water. For instance, **7-A** can be converted to 4-hydroxy azaisoindoline **7-B** using KOH in the presence of $Pd_2(dba)_3$ and *t*BuXphos in 1,4-dioxane and water. O-Alkylation of **7-B** with **5-A** can be accomplished using the general procedures described in Scheme 5 and 6 (see **4-G** to **5-B**). The protecting group (PG2 = Cbz or Boc) of **7-C** can be removed using the general procedures for removing Cbz or Boc as described in Scheme 5 (see **5-B** to **5-C**) to afford **7-D**. This can be converted to **7-F** as described in Scheme 5 (see **5-C** to **5-E**). Removal of the protecting group (PG1 = Boc or Bn) of **7-F** affords **7-G** (see **5-B** to **5-C**)**.** Subsequent *N*-alkylation, as discussed in Scheme 5 (see **5-F** to **5-G**), affords **7-H**. The resulting amines **7-G** and **7-H** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

Scheme 8



Scheme 8 illustrates the general methods for converting compound **8-A** into **8-E** and **8-F** (X and Y = N and/or CH). The chloro group of **1-H** can be displaced with amine **8-A** in the presence of an acid scavenger, usually Et_3N or $(i\text{-}Pr)_2NEt$, in a solvent like IPA, *tert*-BuOH, n-BuOH, *tert*-amyl alcohol, CH_2Cl_2, THF, DMF, or isopropyl acetate, to afford **8-B**. Subsequently, **8-B** can be converted to compound **8-D** by reaction with **8-C**, using a strong base, such as KOtBu or sodium hydride, in neutral solvent like THF, DMF, DMSO or NMP. The protecting group (PG = Boc or Bn) of **8-D** can be removed using the general procedures for removing Boc or Bn group as described in Scheme 5 (see **5-B** to **5-C**), to afford **8-E**. This compound can be alkylated using a wide range of suitable alkylating agents, as illustrated in Scheme 5 (see **5-F** to **5-G**), to afford **8-F**. The resulting amine **8-E** and **8-F** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

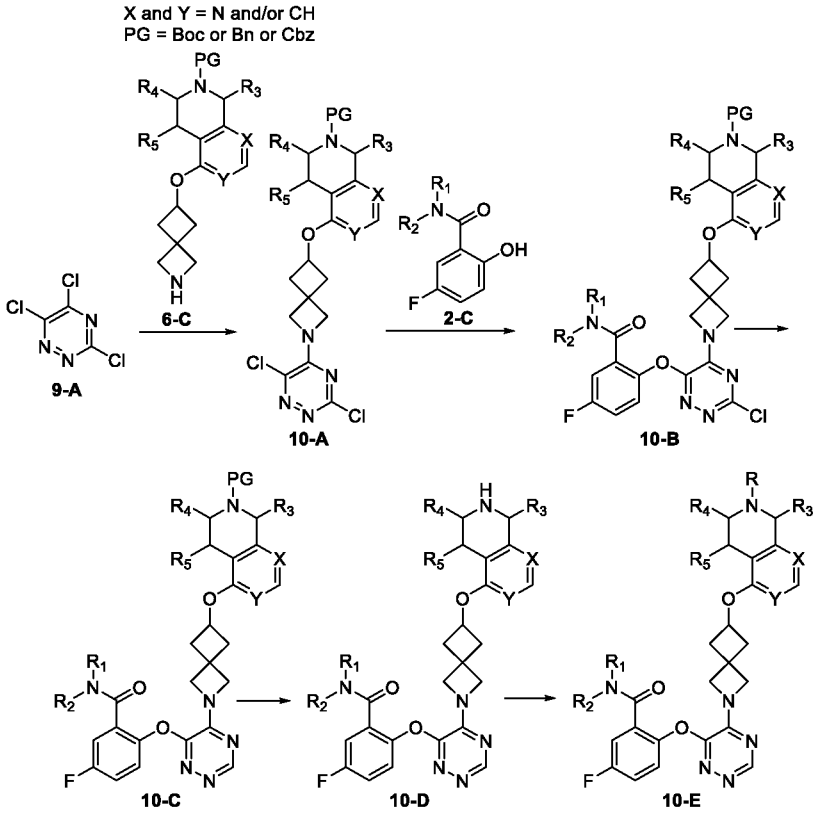
Scheme 9



Scheme 9 illustrates the general methods for converting compound **5-C** into **9-E** and **9-F** (X and Y = N and/or CH). Under suitable conditions, 3,5,6-trichloro-1,2,4-triazine (**9-A**) can be reacted with various amines to afford the product resulting from the displacement of the chloro-group at the 5-position. For example, compound **9-A** can be reacted with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate to afford compound **9-B**. Typically, this reaction is conducted in the presence of a suitable base, such as Et_3N or $(i\text{-}Pr)_2NEt$, and in a neutral solvent like CH_2Cl_2, THF or NMP. Under appropriate conditions, phenol **2-C** can react with compound **9-B** to afford compound **9-C**, *via* displacement of the chloro-group at the 6-position of **9-B**. This reaction is conducted in the presence of a suitable base, oftentimes DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), in a neutral solvent, such as THF. Many different acid scavengers, for example Et_3N, $(i\text{-}Pr)_2NEt$, or pyridine, in a neutral solvent like CH_2Cl_2 or dioxane, can be used to achieve this type of

transformation. Those of skill in the art will recognize that competing displacement of the chloro-group at the 3-position might also occur, to varying degrees, during this reaction. As desired, the chloro-group at the 3-position of compound **9-C** can be retained, displaced by a nucleophile, or removed to afford compound **9-D**. Removal of the chloro group and the protecting group (where PG = benzyl) of **9-C** is typically accomplished in one pot under reductive conditions to afford compounds of the present invention **9-E**. This transformation is oftentimes achieved by reaction with hydrogen gas in the presence of a catalyst like Pd-C, $Pd(OH)_2/C$, Raney Nickel, Ru/C or Ir/C, in a suitable solvent, usually methanol, ethanol, 2,2,2-trifluoroethanol, ethyl acetate, or a combination thereof. When PG = Boc, hydrogenation will remove the chloro group but leave the Boc protecting group. The dechlorination reaction can also be accomplished using a metal hydride like $NaBH_4$, $LiBH_4$ or 9-BBN, generally in the presence of a palladium catalyst, like $Pd(dppf)Cl_2$ or $Pd(OAc)_2$. Removal of the Boc group of **9-D** to affords **9-E**, and subsequent *N*-alkylation, as illustrated in Scheme 5 (see **5-F** to **5-G**), affords **9-F** (R = an appropriate alkyl group). The resulting amines **9-E** and **9-F** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

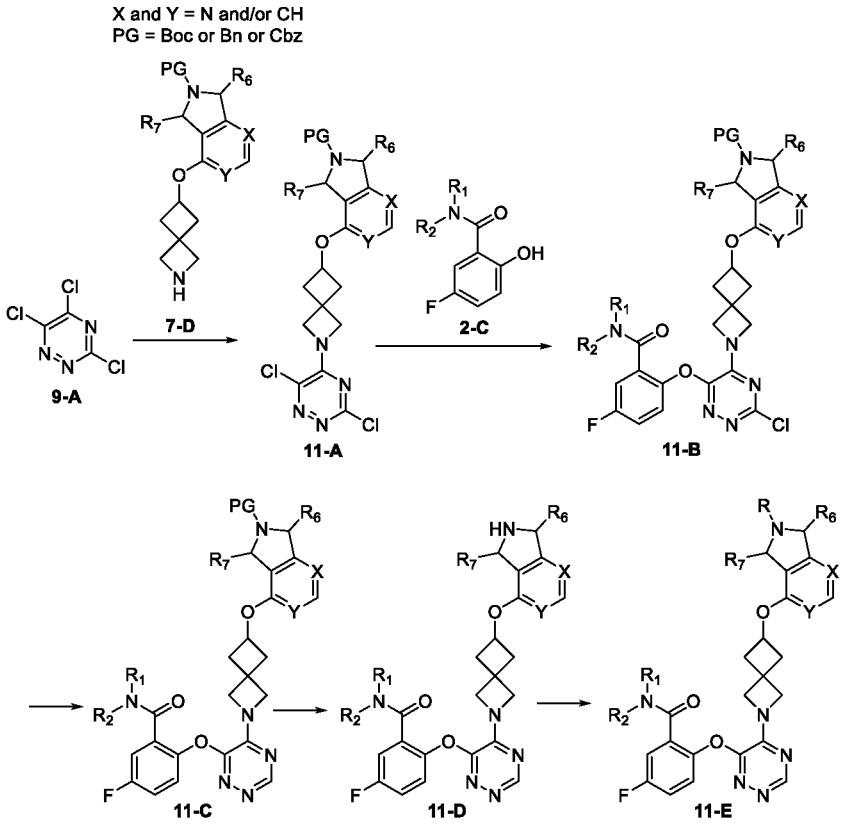
Scheme 10



Scheme 10 illustrates the general methods for converting compound **6-C** into **10-D** and **10-E** (X and Y = N and/or CH). Chloro displacement at the 5-position with various amines **6-**

C affords products **10-B**, as described in Scheme 9 (see **9-A** to **9-B**). Under suitable conditions, as described in Scheme 9 (see **9-B** to **9-C**), phenol **2-C** will react with compound **10-A** to afford compound **10-B**. Removal of the chloro-group and the protecting group (where PG = Bn or Boc) of **10-B** can be accomplished as illustrated in Scheme 9 (**9-C** to **9-E**), to afford compounds **10-D**. *N*-Alkylation, as described in Scheme 5 (see **5-F** to **5-G**), affords **10-E** (R = an appropriate alkyl group). The resulting amines **10-D** and **10-E** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

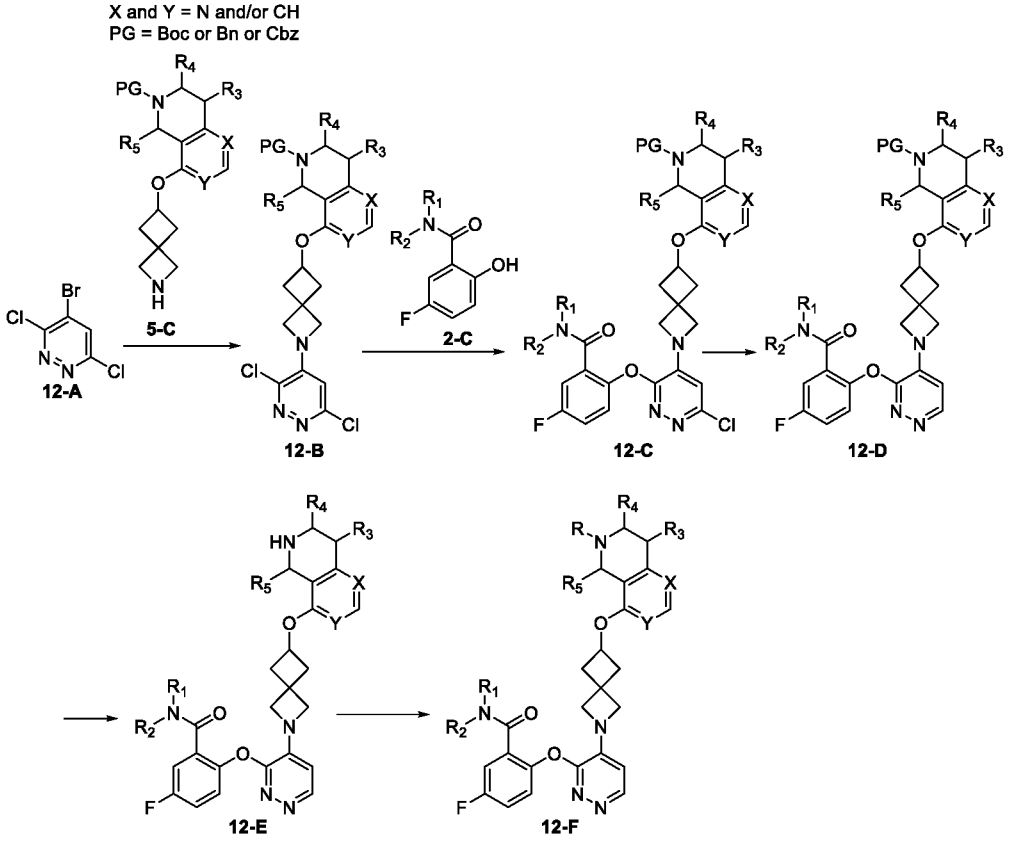
Scheme 11



Scheme 11 illustrates the general methods for converting compound **7-D** into **11-D** and **11-E** (X and Y = N and/or CH). Chloro displacement at the 5-position with various amines **7-D** to afford the product **11-A** can be accomplished using the general procedures described in Scheme 9 (see **9-A** to **9-B**). Under the general conditions described in Scheme 9 (see **9-B** to **9-C**), phenol **2-C** can react with compound **11-A** to afford compound **11-B**, *via* displacement of the chloro-group at the 6-position of **11-A**. Removal of the chloro-group and the protecting group (where PG = benzyl or Boc) of **11-B** can be accomplished as illustrated in Scheme 9 (**9-C** to **9-E**), to afford compounds **11-D**. Subsequent *N*-alkylation using a wide range of alkylating agents, as described in Scheme 5 (see **5-F** to **5-G**), affords compounds **11-E** (R = an appropriate

alkyl group). The resulting amines **11-D** and **11-E** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

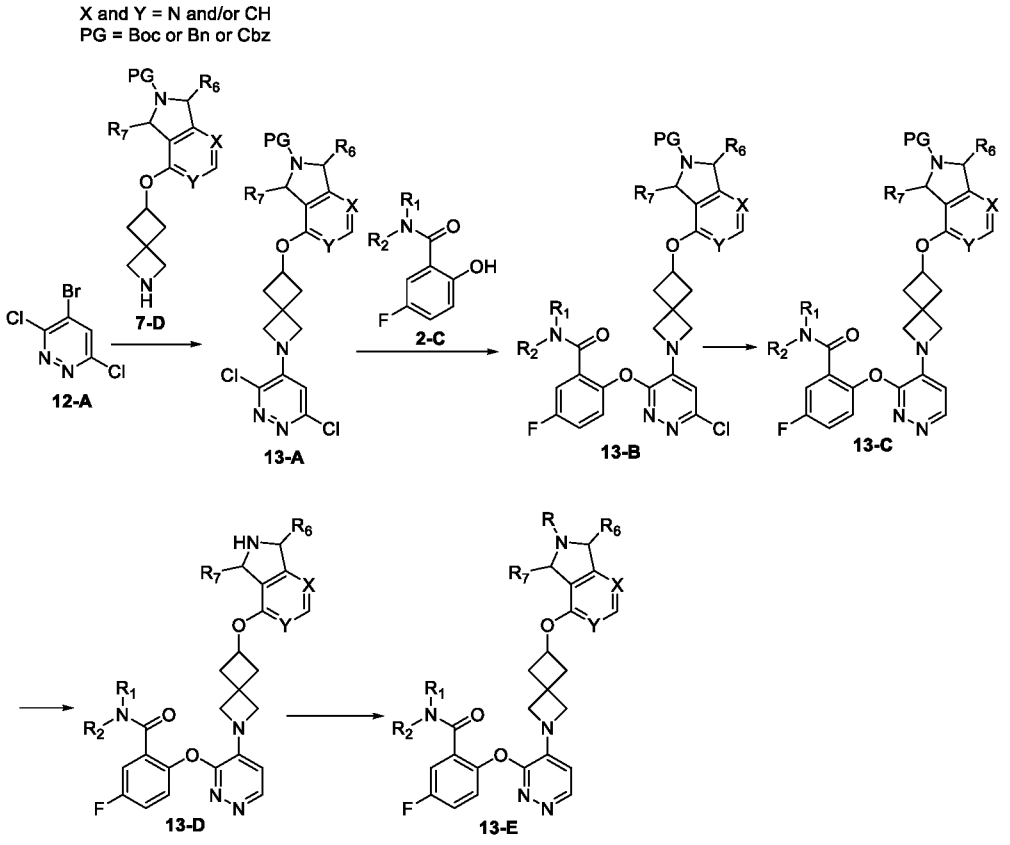
Scheme 12



Scheme 12 illustrates the general methods for converting compound **5-C** into the compounds **12-E** and **12-F** (X and Y = N and/or CH). Bromo displacement at the 4-position with various amines **5-C**, to afford the product **12-B**, can be accomplished using the general procedures described in Scheme 9 (see **9-A** to **9-B**). For instance, **12-A** is reacted with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate in the presence of K_2CO_3 in DME to afford **12-B**. Under the general conditions described in Scheme 9 (see **9-B** to **9-C**), **2-C** can react with **12-B** to afford compound **12-C**. For example, *tert*-butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate **12-B** is reacted with *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide **2-C** in the presence of a suitable base, K_2CO_3, in 1,4-dioxane, to afford corresponding compound **12-C**. Removal of the chloro group and the protecting group (where PG = benzyl) of **12-C** is typically accomplished in one pot under reductive conditions, as generally described previously, to afford compounds **12-E**. Removal of the Boc group of **12-D** to afford compounds **12-E** is accomplished as described in Scheme 5 (see **5-E** to **5-G**). Subsequent *N*-alkylation can be accomplished using a wide range of appropriate alkylating

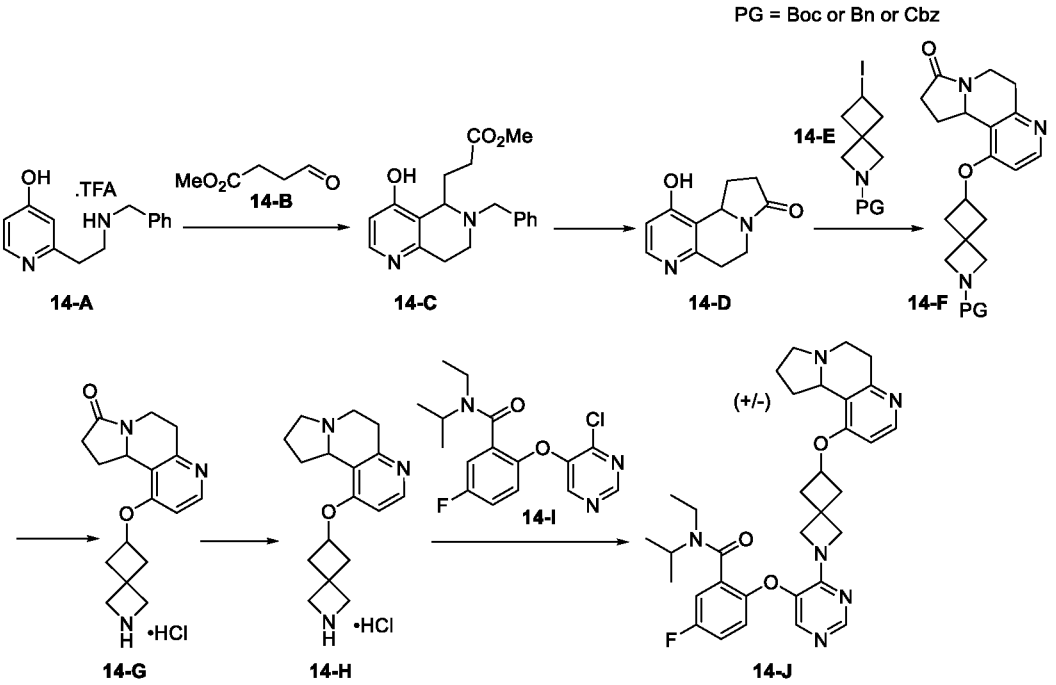
agents, as illustrated in Scheme 5 (see **5-F** to **5-G**), to afford the compounds **12-F** (R = an appropriate alkyl group). The resulting amine **12-E and 12-F** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

Scheme 13



Scheme 13 illustrates the general methods for converting compound **7-D** into the compounds **13-D** and **13-E** (X and Y = N and/or CH). Bromo displacement at the 4-position with various amines **8-C** to afford **13-B** can be accomplished using the general procedures described in Scheme 12 (see **12-A** to **12-B**). Under the general conditions outlined in Scheme 12 (see **12-B** to **12-C**), **2-C** can react with compound **13-A** to afford **13-B**. Removal of the chloro group and the protecting group (where PG = benzyl or Boc) of **13-B** can be accomplished, as illustrated in Scheme 12 (**12-C** to **12-E**), to afford compounds of the present invention **13-D**. This compound can be then *N*-alkylated using a wide range of appropriate alkylating agents, as illustrated in Scheme 5 (see **5-F** to **5-G**), to afford the compounds **13-E** (R = an appropriate alkyl group). The resulting amines **13-D** and **13-E** can be isolated as the free base or as a suitable salt form, as is discussed in Scheme 5.

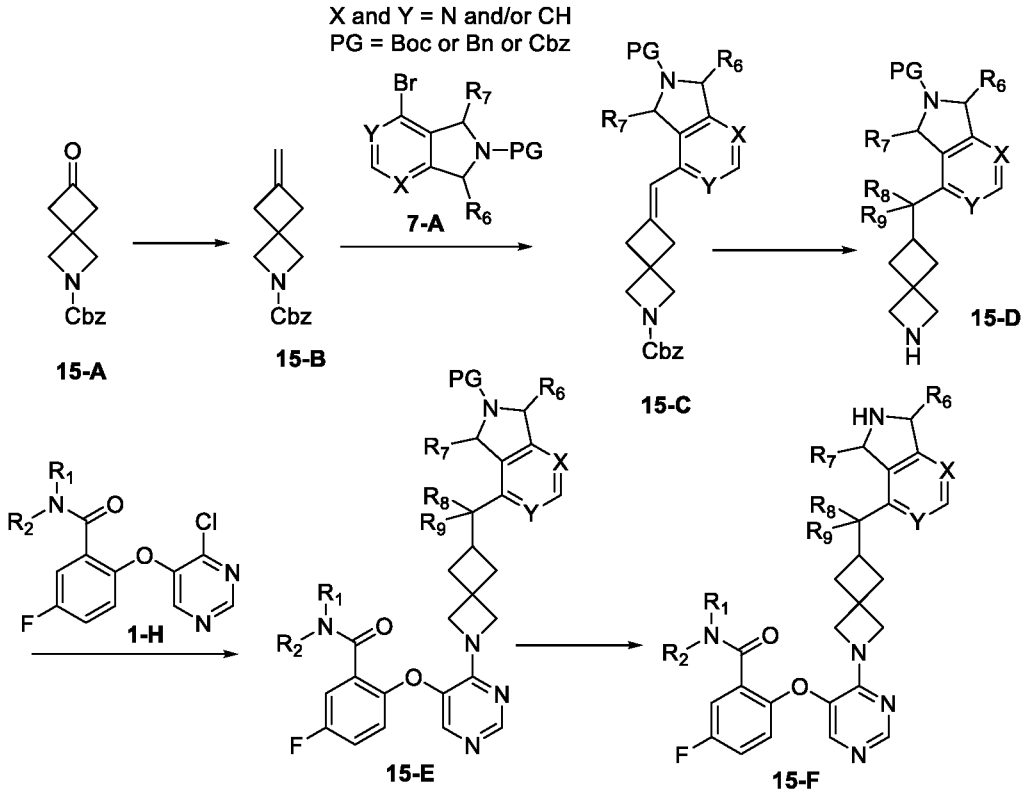
Scheme 14



Scheme 14 illustrates the general methods for converting compound **14-A** into compounds **14-J**. Compound **14-A** can be reacted with aldehydes in a Pictet-Spengler-type reaction, according to the general procedures described in Schemes 4 (see **4-E** to **4-F**). For example, reaction of **14-A** with methyl 4-oxobutanoate in DMSO affords the tetrahydronaphthyridine derivative **14-C.** The benzyl group on the basic nitrogen of **14-C** can be removed by hydrogenolysis, typically using hydrogen gas with a palladium catalyst (oftentimes palladium on activated carbon), in the presence of catalytic acetic acid, in MeOH or ethanol as solvent. The resulting free amine (not shown in the scheme) typically reacts with the ester *in situ* to afford the lactam product **14-D**. **14-D** can be O-alkylated using a suitable alkylating reagent, following the general methods described in Scheme 5 (see **4-G** to **5-B**). Preferably, **14-D** can be reacted with **14-E** (*tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate) under basic conditions, such as K_2CO_3, in a neutral solvent, DMF, at elevated temperature, to afford **14-F**. The protecting group (Boc or Bn) of **14-F** can be removed using the general procedures for removing a Boc or Bn protecting group described in Scheme 5 (see **5-B** to **5-C**), to afford **14-G**. The amide group of **14-G** can be subsequently reduced to the corresponding amine. Many different conditions have been developed to achieve this type of transformation and will be generally familiar to those of skill in the art. Typically, this transformation is accomplished using stoichiometric reductants such as aluminum or boron hydrides ($LiAlH_4$, $BH_3.Et_2O$, $BH_3.DMS$, or 9-BBN) in solvents such as THF, Et_2O, DCM, hexane or toluene. For instance, the amide group of **14-G** can be reduced to the amine **14-H**

using $LiAlH_4$ in THF. Alternatively, the amide can be reduced to the corresponding amine by initial amide activation using, for instance, Tf_2O (trifluoromethanesulfonic anhydride) in the presence of an acid scavenger like 2-fluoropyridine, or a Lewis acid, such as $BF_3.Et_2O$, followed by reduction with a reducing agent like $NaBH_4$ or tetramethyldisiloxane. The resulting amine **14-G** and **14-H** can be isolated as the free base or as a suitable salt form, as discussed in Scheme 5. **14-H** is then converted to **14-J** according to the general methods described previously (see earlier Schemes).

Scheme 15



Scheme 15 illustrates the general methods for converting compound **15-A** into the compounds **15-F** (X and Y = N and/or CH). The ketone of compound **15-A** can be converted to an olefin (**15-B**) using well-known methods like the Wittig reaction (using a suitable phosphonium ylide reagent), the Julia olefination (using an appropriate sulfone reagent), and the Peterson olefination (using an appropriate silyl reagent). In a representative example, **15-A** is reacted with methylenetriphenylphosphorane (prepared *in situ* from methyltriphenylphosphonium bromide using a base like KO*t*-Bu or NaO*t*-Bu) in a neutral solvent like THF or toluene. Compound **15-B** can be coupled with the bromo compound **7-A** using a Heck-type coupling reaction. This type of reaction is typically run using an appropriate Pd catalyst, oftentimes $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(dba)_3$ or $Pd(dppf)Cl_2$, in combination with suitable phosphine ligand, such as XPhos, Xantphos, BINAP, RuPhos or Brettphos. The

reduction of the olefin of **15-C**, with concomitant Cbz-deprotection, can be achieved under hydrogenation conditions, to afford compound **15-D**. Typically, this transformation is accomplished by reaction with hydrogen gas in the presence of a palladium catalyst, such as palladium on activated carbon (Pd/C) or $Pd(OH)_2$, in a suitable solvent, usually methanol, ethanol, ethyl acetate, or a combination thereof. Sometimes, PtO_2 is used as a hydrogenation catalyst. Compound **15-D** can be converted to compound **15-E** *via* chloro displacement, as described previously (see earlier Schemes). Removal of the protecting group (Boc or Bn) of **15-E** can be accomplished by following the general procedures described in Scheme 5 (see **5-B** to **5-C**) to afford the compounds **15-F** (X and Y = N and/or CH).

General Biological Methods

Menin-MLL Competition and MV4;11 Cell Proliferation Assays

Menin-MLL is a competition assay between human Menin and N-terminal portion of human MLL representing amino acids 4-43 of the protein. The interaction between Menin and MLL peptide was monitored by HTRF employing Terbium labeled anti-His6 antibody directed to the N-terminal His6-tag on recombinant Menin and FITC group covalently attached to the MLL peptide. The N-terminal fragment of MLL, retained in all MLL fusion proteins, is involved in the interactions with Menin, and this protein-protein interaction is critical for the MLL fusion proteins mediated leukemogenic transformations.

For IC_{50} determination test compounds may be prepared as stock solutions. Lower sub-stocks of 50μM may be prepared from the 10mM stock solution. To test the compounds in assay, 3.16-fold serial dilutions are made in 100% DMSO. Mid-stock of 50x compounds (50μM) were serially diluted (3.16 fold) in 100% DMSO in Polypropylene plate. In assay plate 1 micro-litre of the previously prepared compound dilution was stamped. H-FL-Menin diluted to 4nM in assay buffer (50 mM Tris-HCl, pH 7.4, 50 mM NaCl, freshly prepared 1 mM DTT, 0.01% BSA, 0.005% Triton X-100) was pre-incubated with 8nM anti-His6-Tb for 30 min at room temperature. FITC-MLL-4-43 was diluted to 2nM in assay buffer and 25 μL was dispensed into each well of the assay plate followed by addition of 25μl of pre-incubated H-FL-Menin and anti-His6-Tb mixture. Final concentration H-FL-Menin diluted to 1nM in assay plate with 2nM anti-His6-Tb and 1nM FITC-MLL-4-43. After 1 hr incubation at room temperature, the HTRF signal was measured on the Spark multi-label plate reader. Resulting data were captured as a ratio of RFU520/RFU485 × 1000. The max values were obtained from 0% inhibition in presence of 2% DMSO and the min. values were 100% inhibition in presence of 1μM reference compound.

Cell Proliferation Assay – MV4;11

Compounds were evaluated for its capacity to inhibit the proliferation of the MLLr leukemia cell line MV4-11 that harbors an MLL1-AF4 fusion protein. MV4-11 cells were cultured for 72 hours with limiting dilutions of compounds and viability was measured using CellTiter-Glo.

Compounds were dissolved to obtain as 10mM solution in DMSO. The stock was diluted 1:5 to the top concentration of 2mM in 100% DMSO. For IC_{50} determination, serial 1:3.16 dilutions were prepared in 100% DMSO by diluting 20µL into 43.5µL of DMSO for 8 concentrations. Each prepared DMSO solution were further diluted 1:500 in the cell culture media to obtain the 2x dosing solutions. The final concentrations of tested compounds in the cell culture media ranged from 0.632nM to 2000nM.

MV4-11 cells were cultured in IMDM with 10% FBS and 1x Penicillin-Streptomycin at 5% CO_2 and 37°C. A cell suspension was prepared containing 15,000cells/ml in the culture medium and 100µL of this suspension was added per well to a 96-well cell culture plate. Then, 100 µL of 2x dosing media containing test compounds were added bringing the total volume to 200µL. These cells were cultured for 72 hours at 37°C and 5% CO_2 in a humidified incubator.

After 72 hours, the cultured cells were mixed and 100µL was transferred to a 96-well black plate. Cell Titer Glo (100 µl) was then added to this plate. The plate was mixed with shaking for 15 mins at RT, the luminescence was then measured using Tecan Spark 20M spectrophotometer. Cell Viability (%) was determined by RLU of test/RLU average vehicle control*100 and % max inhibition was determined by 100-(% cell viability remaining at the top concentration of compound).

hERG Patch Clamp Assay

The hERG inhibition assay uses a high throughput single cell planar patch clamp approach. Chinese hamster ovary cells transfected with the hERG gene (CHO-hERG) are dispensed into the PatchPlate. Amphotericin is used as a perforating agent to gain electrical access to the cells. The hERG tail current is measured prior to the addition of the test compound by perforated patch clamping. Following addition of the test compound at a defined concentration or range of concentrations a second recording of the hERG current is performed. The degree of inhibition (%) is obtained by measuring the tail current amplitude, which is induced by a one second test pulse to - 40 mV after a two second pulse to + 20 mV, before and after drug incubation (the difference current is normalized to control and multiplied by 100 to obtain the percent of inhibition). The patch clamp assay can be used according to the knowledge

of a person of ordinary skill in the art to accordingly assess the compounds of the present disclosure.

In any one of the embodiments described herein, the compound has an IC_{50} of more than 10, 15, 20, 25, or 30 μM in a standard human ether-a-go-go related gene (hERG) patch clamp assay.

A number of drugs have been withdrawn from late-stage clinical trials due to cardiotoxic effects, therefore it is important to identify and avoid compounds with potential for cardiotoxic effects early in drug discovery. The cardiovascular toxicity of a compound can be measured using a standard human ether-a-go-go related gene (hERG) assay. The human ether-a-go-go related gene (hERG) encodes the inward rectifying voltage gated potassium channel in the heart (IKr), which is involved in cardiac repolarization. Inhibition of the hERG current causes QT interval prolongation resulting in potentially fatal ventricular tachyarrhythmia called Torsade de Pointes. A compound having an IC50 of more than about 10 μM or more than about 15 μM, in the hERG assay may be considered as free from any cardiovascular toxicity. In some embodiments, the compounds of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and/or Table 1 have reduced hERG binding compared to structural analogs. In some embodiments, the compounds of Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and/or Table 1 IC_{50} of more than 10 μM, 15 μM, 20 μM, 25 μM, or 30 μM in the standard patch clamp hERG assay.

In some embodiments, the compounds of the present disclosure (e.g., Formulae I, Ia, Ib, Ic, Id, Ie, If, II, IIa, IIb, IIc, IId, IIe, IIf, and III, and Table 1) do not significantly block the hERG potassium channel (e.g., an IC_{50} greater than 1 μM, μM, 10 μM, 15 μM, 20 μM, 25 μM, 30 μM, 35 μM, 40 μM, or 50 μM) in the standard patch clamp hERG assay.

Methods of Use

The compounds of the invention are inhibitors of the interaction of menin with MLL and MLL fusion proteins. In some embodiments, the present disclosure is directed to a method of inhibiting the interaction between menin and MLL or an MLL fusion protein by contacting menin and MLL or the MLL fusion protein with a compound of the disclosure. The contacting can be carried out *in vitro* or *in vivo*. In some embodiments, the compounds of the disclosure can bind to menin, thereby interfering with the binding of MLL to menin. In some embodiments, the present disclosure provides a method of inhibiting the activity of menin by contacting menin with a compound of the disclosure in the presence of MLL or an MLL fusion protein. In further embodiments, the present disclosure provides a method of inhibiting the

binding of MLL or an MLL fusion protein to menin, comprising contacting menin with a compound of the disclosure in the presence of the MLL or MLL fusion protein.

In some embodiments, compounds of the present disclosure minimize hERG interactions. In some embodiments, the present disclosure is directed to a method of inhibiting the interaction between menin and MLL or an MLL fusion protein by contacting menin and MLL or the MLL fusion protein with a compound of the disclosure while the compounds of the disclosure minimize hERG activity. In some embodiments, the present disclosure is directed to a method of inhibiting the interaction between menin and MLL or an MLL fusion protein by contacting menin and MLL or the MLL fusion protein with a compound of the disclosure while the compound of the disclosure avoids drug-induced blockade of hERG.

Evaluating the hERG activity can be accomplished by many methods known in the art. Including, such methods for the assessment of hERG liability is the patch-clamp electrophysiological assay on hERG transfected cells. Various other strategies including radiolabeled binding assays, functional assays, and rubidium efflux assays also quantify hERG potency.

The compounds of the disclosure are also useful in treating diseases associated with the menin-MLL interaction or menin-MLL fusion protein interaction. For example, diseases and conditions treatable according to the methods of the disclosure include cancer, such as leukemia, and other diseases or disorders mediated by the menin-MLL interaction or menin-MLL fusion protein interaction such as diabetes.

Accordingly, the compounds of the disclosure are believed to be effective against a broad range of cancers, including, but not limited to, hematological cancer (*e.g.*, leukemia and lymphoma), bladder cancer, brain cancer (*e.g.*, glioma, diffuse intrinsic pontine glioma (DIPG)), breast cancer (*e.g.*, triple-negative breast cancer, estrogen-receptor-positive breast cancer (*i.e.*, ER+ breast cancer)), colorectal cancer, cervical cancer, gastrointestinal cancer (*e.g.*, colorectal carcinoma, gastric cancer), genitourinary cancer, head and neck cancer, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer (*e.g.*, castration resistant prostate cancer), renal cancer (*e.g.*, renal cell carcinoma), skin cancer, thyroid cancer (*e.g.*, papillary thyroid carcinoma), testicular cancer, sarcoma (*e.g.*, Ewing's sarcoma), and AIDS-related cancers. In some embodiments, the cancer is associated with a rearranged MLL gene. In some embodiments, the pathophysiology of the cancer is dependent on the MLL gene. In some embodiments, the cancer is associated with mutant p53 gain-of-function.

In some embodiments, the specific cancers that may be treated by the compounds, compositions and methods described herein include cardiac cancers, such as for example, sarcoma (*e.g.*, angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; lung cancers, including, for example, bronchogenic carcinoma (*e.g.*, squamous cell, undifferentiated small cell, undifferentiated large cell, and adenocarcinoma), alveolar and bronchiolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell lung cancer, small cell lung cancer, bronchial adenomas/carcinoids, and pleuropulmonary blastoma; gastrointestinal cancer, including, for example, cancers of the esophagus (*e.g.*, squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma), cancers of the stomach (*e.g.*, carcinoma, lymphoma, and leiomyosarcoma), cancers of the pancreas (*e.g.*, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, and vipoma), cancers of the small bowel (*e.g.*, adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma), cancers of the large bowel or colon, (*e.g.*, adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, and leiomyoma), and other cancers of the digestive tract (*e.g.*, anal cancer, anorectal cancer, appendix cancer, cancer of the anal canal, cancer of the tongue, gallbladder cancer, gastrointestinal stromal tumor (GIST), colon cancer, colorectal cancer, extrahepatic bile duct cancer, intrahepatic bile duct cancer, rectal cancer, and small intestine cancer); genitourinary tract cancers, including, for example, cancers of the kidney (*e.g.*, adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, and leukemia), cancers of the bladder and urethra (*e.g.*, squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma), cancers of the prostate (*e.g.*, adenocarcinoma and sarcoma), cancers of the testis, (*e.g.*, seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, and lipoma), as well as transitional cell cancer, transitional cell cancer of the renal pelvis and ureter and other urinary organs, urethral cancer, and urinary bladder cancer; liver cancers, including, for example, hepatoma (*e.g.*, hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma; bone cancers, including, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochrondroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; nervous system cancers, including, for example, cancers of the skull (*e.g.*, osteoma,

hemangioma, granuloma, xanthoma, and osteitis deformans); cancers of the meninges (*e.g.*, meningioma, meningiosarcoma, and gliomatosis); cancers of the brain (*e.g.*, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, and congenital tumors); cancers of the spinal cord (*e.g.*, neurofibroma, meningioma, glioma, and sarcoma), and other nervous system cancers (e.g., brain stem glioma, diffuse intrinsic pontine glioma (DIPG), brain tumor, central nervous system cancer, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, childhood cerebellar astrocytoma, childhood cerebral astrocytoma, primary central nervous system lymphoma, visual pathway and hypothalamic glioma, nervous system lymphoma, supratentorial primitive neuroectodeimal tumors, pineoblastoma and supratentorial primitive neuroectodermal tumors); gynecological cancers, including, for example, cancers of the uterus (*e.g.*, endometrial carcinoma), cancers of the cervix (*e.g.*, cervical carcinoma, and pre tumor cervical dysplasia), cancers of the ovaries (*e.g.*, ovarian carcinoma, including serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa thecal cell tumors, Sertoli Leydig cell tumors, dysgerminoma, and malignant teratoma), cancers of the vulva (*e.g.*, squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma), cancers of the vagina (*e.g.*, clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma, and embryonal rhabdomyosarcoma), and cancers of the fallopian tubes (*e.g.*, carcinoma); other reproductive tract cancers, including, for example, endometrial cancer, endometrial uterine cancer, germ cell tumor, gestational trophoblastic tumor, gestational trophoblastic tumor glioma, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, penile cancer, vaginal cancer, vulvar cancer, extracranial germ cell tumor, extragonadal germ cell tumor, uterine cancer, uterine corpus cancer, uterine sarcoma; lymphatic and hematologic cancers, including, for example, cancers of the blood (*e.g.*, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, and myelodysplastic syndrome, Hodgkin's lymphoma, non Hodgkin's lymphoma (malignant lymphoma) and Waldenstrom's macroglobulinemia), and other lymphatic or hematologic cancers including, for example, childhood leukemia, myeloproliferative disorders (*e.g.*, primary myelofibrosis), plasma cell neoplasm/multiple myeloma, myelodysplasia, myelodysplastic syndrome, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymoma and thymic carcinoma, mycosis fungoides, and Sézary Syndrome; skin cancers, including, for example, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles

dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, merkel cell carcinoma, merkel cell skin carcinoma, melanoma, and carcinoid tumor; adrenal gland cancers, including, for example, neuroblastoma; other cancers associated with the endocrine system including, for example, adrenocortical carcinoma, multiple endocrine neoplasia (*e.g.*, multiple endocrine neoplasia type I), multiple endocrine neoplasia syndrome, parathyroid cancer, pituitary tumor, pheochromocytoma, islet cell pancreatic cancer, and islet cell tumors); connective tissue cancer (*e.g.*, bone cancer, bone and joint cancer, osteosarcoma and malignant fibrous histiocytoma); cancer associated with the head, neck, and mouth (*e.g.*, head and neck cancer, paranasal sinus and nasal cavity cancer, metastatic squamous neck cancer, mouth cancer, throat cancer, esophageal cancer, laryngeal cancer, pharyngeal cancer, hypopharyngeal cancer, lip and oral cavity cancer, nasopharyngeal cancer, oral cancer, oropharyngeal cancer, and salivary gland cancer); and cancer associated with the eye (*e.g.*, ocular cancer, intraocular melanoma). In some embodiments, the cancer is Ewing's sarcoma.

In some embodiments, the cancer is a hematological cancer such as leukemia or lymphoma. Example leukemia and lymphomas treatable by the compounds of the disclosure include mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL-r), leukemia associated with a MLL rearrangement or a rearrangement of the *MLL* gene, acute leukemia, chronic leukemia, indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL) (also referred to as acute lymphoblastic leukemia or acute lymphoid leukemia), acute myeloid leukemia (AML) (also referred to as acute myelogenous leukemia or acute myeloblastic leukemia), acute granulocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL) (also referred to as chronic lymphoblastic leukemia), chronic myelogenous leukemia (CML) (also referred to as chronic myeloid leukemia), therapy related leukemia, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD) (such as primary myelofibrosis (PMF)), myeloproliferative neoplasia (MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sézary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma (malignant lymphoma), and Waldenstrom's macroglobulinemia. In some embodiments, the

acute myeloid leukemia (AML) is abstract nucleophosmin (NPM1)-mutated acute myeloid leukemia (*i.e.*, $NPM1^{mut}$ acute myloid leukemia).

In particular embodiments, compounds of the disclosure are used to treat leukemia associated with a MLL rearrangement, acute lymphocytic leukemia associated with a MLL rearrangement, acute lymphoblastic leukemia associated with a MLL rearrangement, acute lymphoid leukemia associated with a MLL rearrangement, acute myeloid leukemia associated with a MLL rearrangement, acute myelogenous leukemia associated with a MLL rearrangement, or acute myeloblastic leukemia associated with a MLL rearrangement. As used herein, "MLL rearrangement" means a rearrangement of the *MLL* gene.

In some embodiments, diseases and conditions treatable with compounds of the disclosure include insulin resistance, pre-diabetes, diabetes (*e.g.*, Type 2 diabetes or Type 1 diabetes), and risk of diabetes. In some embodiments, diseases and conditions treatable with compounds of the disclosure include hyperglycemia. In some embodiments, the hyperglycemia is associated with diabetes, such as Type 2 diabetes. In some embodiments, compounds of the disclosure are used to treat loss of response to other anti-diabetic agents and/or reduced beta cell function in a patient or subject. In some embodiments, compounds of the disclosure are used to restore response to other anti-diabetic agents and/or to restore beta cell function and/or to reduce the need for insulin in a patient or subject. In some embodiments, compounds of the disclosure are used to reduce insulin resistance, reduce the risk of diabetes, or reduce increases in blood glucose caused by a statin in a subject taking a statin. In some embodiments, compounds of the disclosure are used to treat diabetes in a subject taking a statin or to prevent diabetes in a subject taking a statin. Methods of the disclosure include decreasing, reducing, inhibiting, suppressing, limiting or controlling in the patient elevated blood glucose levels. In further aspects, methods of the disclosure include increasing, stimulating, enhancing, promoting, inducing or activating in the subject insulin sensitivity. Statins include, but are not limited to atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rousuvastatin and simvastatin.

In some embodiments, a patient is treated with (*e.g.*, administered) a compound of the present disclosure in an amount sufficient to treat or ameliorate one or more of the diseases and conditions recited above (*e.g.*, a therapeutically effective amount). The compounds of the disclosure may also be useful in the prevention of one or more of the diseases recited therein.

Combination Therapy

The disclosure further relates to a combination therapy for treating a disease or a disorder described herein. In some embodiments, the combination therapy comprises

administering at least one compound of the present disclosure in combination with one or more other pharmaceutically active agents for treating cancer or other disorders mediated by menin/MLL. In some embodiments, the combination therapy comprises administering at least one compound of the present disclosure in combination with one or more other pharmaceutically active agents, such as for the treatment of cancer. The pharmaceutically active agents can be combined with a compound of the disclosure in a single dosage form, or the therapeutics can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, the invention provides a combination therapy comprising a menin inhibitor of the present disclosure (*e.g.,* a compound of Formula I, Formula Ia, Formula Ib, Formula Ic, Formula Id, Formula Ie, Formula If, Formula II, Formula IIa, Formula IIb, Formula IIc, Formula IId, Formula IIe, Formula IIf, Formula III, etc.) and a CYP3A4 inhibitor. In certain embodiments, the invention provides for a pharmaceutical composition comprising: (a) a menin inhibitor of the present disclosure (*e.g.,* a compound of Formula I, Formula Ia, Formula Ib, Formula Ic, Formula Id, Formula Ie, Formula If, Formula II, Formula IIa, Formula IIb, Formula IIc, Formula IId, Formula IIe, Formula IIf, Formula III, etc.), and (b) a CYP3A4 inhibitor. In some embodiments, the invention is directed to a method for treating a patient comprising (a) administering a menin inhibitor of the present disclosure (*e.g.,* a compound of Formula I, Formula Ia, Formula Ib, Formula Ic, Formula Id, Formula Ie, Formula If, Formula II, Formula IIa, Formula IIb, Formula IIc, Formula IId, Formula IIe, Formula IIf, Formula III, etc.), and (b) administering a CYP3A4 inhibitor.

Some embodiments of this invention are directed to combination therapies designed to treat or manage cancer in a subject, wherein the combination therapies comprise administering a menin inhibitor of the present disclosure (*e.g.,* a compound of Formula I, Formula Ia, Formula Ib, Formula Ic, Formula Id, Formula Ie, Formula If, Formula II, Formula IIa, Formula IIb, Formula IIc, Formula IId, Formula IIe, Formula IIf, Formula III, etc.) in combination with a CYP3A4 inhibitor. In particular, some embodiments of this invention are directed to methods of treating or managing cancer in a subject, comprising administering a menin inhibitor in combination with a therapeutically effective amount of a CYP3A4 inhibitor administered simultaneously, separately or sequentially.

In some embodiments, the CYP3A inhibitor is: an antiarrhythmic; an antihistamine; an azole antifungal; a benzodiazepine; a calcium channel blocker; a HIV antiviral; a HMG CoA Reductase inhibitor; a macrolide antibiotic; a prokinetic; a protease inhibitor; or any combinations thereof. In some embodiments, the CYP3A inhibitor is: posaconazole, alprazolam; amiodarone; amlodipine; aprepitant; aripiprazole; astemizole; atorvastatin;

boceprevir; buspirone; chloramphenicol; chlorpheniramine; cimetidine; ciprofloxacin; cisapride; clarithromycin; cobicistat (GS-9350); analogs or derivatives of cobicistat (GS-9350); cyclosporine; delaviridine; diazepam→3-OH; diethyl-dithiocarbamate; diltiazem; erythromycin; felodipine; fluconazole; fluvoxamine; gestodene; gleevec; grapefruit juice; haloperidol; imatinib; indinavir; itraconazole; ketoconazole; lovastatin; methadone; mibefradil; midazolam; mifepristone; nefazodone; nelfinavir; nifedipine; nisoldipine; nitrendipine; norfloxacin; norfluoxetine; pimozide; quinine; quinidine→3-OH; ritonavir; saquinavir; sildenafil; simvastatin; starfruit; tacrolimus (FK506); tamoxifen; telaprevir; telithromycin; trazodone; triazolam; verapamil; telaprevir; vincristine; voriconazole; or any combinations thereof.

In some embodiments, the CYP3A4 inhibitor is posaconazole, cobicistat (GS-9350) or analogs or derivatives of cobicistat (GS-9350). In some embodiments, the CYP3A4 inhibitor is ketoconazole. In some embodiments, the CYP3A4 inhibitor is ritonavir. In some embodiments, the menin inhibitor and the CYP3A4 inhibitor are in separate dosage forms. In some embodiments, the pharmaceutical composition is in a combined dosage form. In some embodiments, the CYP3A4 inhibitor is posaconazole.

In some embodiments, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the oral bioavailability of the menin inhibitor. The compounds according to the disclosure may also be used in combination with immunotherapies, including but not limited to cell-based therapies, antibody therapies and cytokine therapies, for the treatment of a disease or disorder disclosed herein.

In certain embodiments, compounds according to the disclosure are used in combination with one or more passive immunotherapies, including but not limited to naked monoclonal antibody drugs and conjugated monoclonal antibody drugs. Examples of naked monoclonal antibody drugs that can be used include, but are not limited to, rituximab (Rituxan®), an antibody against the CD20 antigen; trastuzumab (Herceptin®), an antibody against the HER2 protein; alemtuzumab (Lemtrada®, Campath®), an antibody against the CD52 antigen; cetuximab (Erbitux®), an antibody against the EGFR protein; and bevacizumab (Avastin®) which is an anti-angiogenesis inhibitor of VEGF protein.

Examples of conjugated monoclonal antibodies that can be used include, but are not limited to, radiolabeled antibody ibritumomab tiuxetan (Zevalin®); radiolabeled antibody tositumomab (Bexxar®); and immunotoxin gemtuzumab ozogamicin (Mylotarg®) which contains calicheamicin; BL22, an anti-CD22 monoclonal antibody-immunotoxin conjugate;

radiolabeled antibodies such as OncoScint® and ProstaScint®; brentuximab vedotin (Adcetris®); ado-trastuzumab emtansine (Kadcyla®, also called TDM-1).

Further examples of therapeutic antibodies that can be used include, but are not limited to, REOPRO® (abciximab), an antibody against the glycoprotein IIb/IIIa receptor on platelets; ZENAPAX® (daclizumab) an immunosuppressive, humanized anti-CD25 monoclonal antibody; PANOREX™, a murine anti-17-IA cell surface antigen IgG2a antibody; BEC2, a murine anti-idiotype (GD3 epitope) IgG antibody; IMC-C225, a chimeric anti-EGFR IgG antibody; VITAXIN™ a humanized anti-αVβ3 integrin antibody; Campath 1H/LDP-03, a humanized anti CD52 IgG1 antibody; Smart M195, a humanized anti-CD33 IgG antibody; LYMPHOCIDE™, a humanized anti-CD22 IgG antibody; LYMPHOCIDE™ Y-90; Lymphoscan; Nuvion® (against CD3; CM3, a humanized anti-ICAM3 antibody; IDEC-114 a primatized anti-CD80 antibody; IDEC-131 a humanized anti-CD40L antibody; IDEC-151 a primatized anti-CD4 antibody; IDEC-152 a primatized anti-CD23 antibody; SMART anti-CD3, a humanized anti-CD3 IgG; 5G1.1, a humanized anti-complement factor 5 (C5) antibody; D2E7, a humanized anti-TNF-α antibody; CDP870, a humanized anti-TNF-α Fab fragment; IDEC-151, a primatized anti-CD4 IgG1 antibody; MDX-CD4, a human anti-CD4 IgG antibody; CD20-streptdavidin (+biotin-yttrium 90); CDP571, a humanized anti-TNF-α IgG4 antibody; LDP-02, a humanized anti-α4β7 antibody; OrthoClone OKT4A, a humanized anti-CD4 IgG antibody; ANTOVA™, a humanized anti-CD40L IgG antibody; ANTEGREN™, a humanized anti-VLA-4 IgG antibody; and CAT-152, a human anti-TGF-β_2 antibody.

In certain embodiments, compounds according to the disclosure are used in combination with one or more targeted immunotherapies containing toxins but not an antibody, including but not limited to denileukin diftitox (Ontak®), IL-2 linked to diphtheria toxin.

The compounds according to the disclosure may also be used in combination with adjuvant immunotherapies for the treatment of a disease or disorder disclosed herein. Such adjuvant immunotherapies include, but are not limited to, cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein (MIP)-1-alpha, interleukins (including IL-1, IL-2, IL-4, IL-6, IL-7, IL-12, IL-15, IL-18, IL-21, and IL-27), tumor necrosis factors (including TNF-alpha), and interferons (including IFN-alpha, IFN-beta, and IFN-gamma); aluminum hydroxide (alum); Bacille Calmette-Guérin (BCG); Keyhole limpet hemocyanin (KLH); Incomplete Freund's adjuvant (IFA); QS-21; DETOX; Levamisole; and Dinitrophenyl (DNP), and combinations thereof, such as, for example, combinations of interleukins, for example IL-2, with other cytokines, such as IFN-alpha.

In certain embodiments, compounds according to the disclosure are used in combination with vaccine therapy, including but not limited to autologous and allogeneic tumor cell vaccines, antigen vaccines (including polyvalent antigen vaccines), dendritic cell vaccines, and viral vaccines.

In another embodiment, the present disclosure comprises administering to a subject with cancer an effective amount of a compound of the disclosure and one or more additional anti-cancer therapies selected from: surgery, anti-cancer agents/drugs, biological therapy, radiation therapy, anti-angiogenesis therapy, immunotherapy, adoptive transfer of effector cells, gene therapy or hormonal therapy. Examples of anti-cancer agents/drugs are described below.

In some embodiments, the anti-cancer agents/drug is, for example, adriamycin, aactinomycin, bleomycin, vinblastine, cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin

sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride; palbociclib; Yervoy® (ipilimumab); Mekinist™ (trametinib); peginterferon alfa-2b, recombinant interferon alfa-2b; Sylatron™ (peginterferon alfa-2b); Tafinlar® (dabrafenib); Zelboraf® (vemurafenib); or nivolumab.

The compounds according to the present disclosure can be administered in combination with existing methods of treating cancers, for example by chemotherapy, irradiation, or surgery. Thus, there is further provided a method of treating cancer comprising administering an effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt form thereof, to a subject in need of such treatment, wherein an effective amount of at least one additional cancer chemotherapeutic agent is administered to the subject. Examples of suitable cancer chemotherapeutic agents include any of: abarelix, ado-trastuzumab emtansine, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, bleomycin, bortezombi, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, emtansine, epirubicin, eribulin, erlotinib, estramustine, etoposide phosphate, etoposide, everolimus, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fruquintinib, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, ixabepilone, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, meclorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane,

mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, pamidronate, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pertuzuma, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, sorafenib, streptozocin, sulfatinib, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, volitinib, vorinostat, and zoledronate.

In particular embodiments, compounds according to the disclosure are used in combination with one or more anti-cancer agent selected from methotrexate, paclitaxel albumin-stabilized nanoparticle formulation, ado-trastuzumab emtansine, eribulin, doxorubicin, fluorouracil, everolimus, anastrozole, pamidronate disodium, exemestane, capecitabine, cyclophosphamide, docetaxel, epirubicin, toremifene, fulvestrant, letrozole, gemcitabine, gemcitabine hydrochloride, goserelin acetate, trastuzumab, ixabepilone, lapatinib ditosylate, megestrol acetate, tamoxifen citrate, pamidronate disodium, palbociclib, and pertuzumab for the treatment of breast cancer.

Other anti-cancer agents/drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors; castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;

cryptophycin A derivatives; curacin A; cyclin-dependent kinase inhibitors; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9- dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate;fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone;

oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitors; microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; zanoterone; zilascorb; zinostatin stimalamer; 5-fluorouracil; and leucovorin.

In some embodiments, the anti-cancer agent/drug is an agent that stabilizes microtubules. As used herein, a "microtubulin stabilizer" means an anti-cancer agent/drug which acts by arresting cells in the G2-M phases due to stabilization of microtubules. Examples

of microtubulin stabilizers include ACLITAXEL® and Taxol® analogues. Additional examples of microtubulin stabilizers include without limitation the following marketed drugs and drugs in development: Discodermolide (also known as NVP-XX-A-296); Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA); Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B); Epothilone E; Epothilone F; Epothilone B N-oxide; Epothilone A N-oxide; 16-aza-epothilone B; 21-aminoepothilone B (also known as BMS-310705); 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone); FR-182877 (Fujisawa, also known as WS-9885B), BSF-223651 (BASF, also known as ILX-651 and LU-223651); AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl); AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A); Fijianolide B; Laulimalide; Caribaeoside; Caribaeolin; Taccalonolide; Eleutherobin; Sarcodictyin; Laulimalide; Dictyostatin-1; Jatrophane esters; and analogs and derivatives thereof.

In another embodiment, the anti-cancer agent/drug is an agent that inhibits microtubules. As used herein, a "microtubulin inhibitor" means an anti-cancer agent which acts by inhibiting tubulin polymerization or microtubule assembly. Examples of microtubulin inhibitors include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104); Dolastatin 10 (also known as DLS-10 and NSC-376128); Mivobulin isethionate (also known as CI-980); Vincristine; NSC-639829; ABT-751 (Abbott, also known as E-7010); Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C); Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9); Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356); Auristatin PE (also known as NSC-654663); Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577); LS-4578 (Pharmacia, also known as LS-477-P); LS-4477 (Pharmacia), LS-4559 (Pharmacia); RPR-112378 (Aventis); Vincristine sulfate; DZ-3358 (Daiichi); GS-164 (Takeda); GS-198 (Takeda); KAR-2 (Hungarian Academy of Sciences); SAH-49960 (Lilly/Novartis); SDZ-268970 (Lilly/Novartis); AM-97 (Armad/Kyowa Hakko); AM-132 (Armad); AM-138 (Armad/Kyowa Hakko); IDN-5005 (Indena); Cryptophycin 52 (also known as LY-355703); Vitilevuamide; Tubulysin A; Canadensol; Centaureidin (also known as NSC-106969); T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067); COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261); H10 (Kansas State University); H16 (Kansas State University); Oncocidin A1 (also known as BTO-956 and DIME); DDE-313 (Parker Hughes Institute); SPA-2 (Parker Hughes Institute); SPA-1 (Parker Hughes Institute, also

known as SPIKET-P); 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569); Narcosine (also known as NSC-5366); Nascapine, D-24851 (Asta Medica), A-105972 (Abbott); Hemiasterlin; 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191); TMPN (Arizona State University); Vanadocene acetylacetonate; T-138026 (Tularik); Monsatrol; Inanocine (also known as NSC-698666); 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine); A-204197 (Abbott); T-607 (Tularik, also known as T-900607); RPR-115781 (Aventis); Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin); Halichondrin B; D-64131 (Asta Medica); D-68144 (Asta Medica); Diazonamide A; A-293620 (Abbott); NPI-2350 (Nereus); TUB-245 (Aventis); A-259754 (Abbott); Diozostatin; (-)-Phenylahistin (also known as NSCL-96F037); D-68838 (Asta Medica); D-68836 (Asta Medica); Myoseverin B; D-43411 (Zentaris, also known as D-81862); A-289099 (Abbott); A-318315 (Abbott); HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth); D-82317 (Zentaris); D-82318 (Zentaris); SC-12983 (NCI); Resverastatin phosphate sodium; BPR-0Y-007 (National Health Research Institutes); SSR-250411 (Sanofi); Combretastatin A4; eribulin (Halaven®); and analogs and derivatives thereof.

In further embodiments, compounds according to the disclosure are used in combination with one or more alkylating agents, antimetabolites, natural products, or hormones.

Examples of alkylating agents useful in the methods of the disclosure include but are not limited to, nitrogen mustards (*e.g.*, mechloroethamine, cyclophosphamide, chlorambucil, melphalan, *etc.*), ethylenimine and methylmelamines (*e.g.*, hexamethlymelamine, thiotepa), alkyl sulfonates (*e.g.*, busulfan), nitrosoureas (*e.g.*, carmustine, lomusitne, semustine, streptozocin, *etc.*), or triazenes (decarbazine, *etc.*).

Examples of antimetabolites useful in the methods of the disclosure include but are not limited to folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*, fluorouracil, floxouridine, cytarabine), and purine analogs (*e.g.*, mercaptopurine, thioguanine, pentostatin). Examples of natural products useful in the methods of the disclosure include but are not limited to vinca alkaloids (*e.g.*, vinblastin, vincristine), epipodophyllotoxins (*e.g.*, etoposide, teniposide), antibiotics (*e.g.*, actinomycin D, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin) or enzymes (*e.g.*, L-asparaginase).

Examples of hormones and antagonists useful for the treatment of cancer include but are not limited to adrenocorticosteroids (*e.g.*, prednisone), progestins (*e.g.*, hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens

(*e.g.*, diethlystilbestrol, ethinyl estradiol), antiestrogen (*e.g.*, tamoxifen), androgens (*e.g.*, testosterone propionate, fluoxymesterone), antiandrogen (*e.g.*, flutamide), and gonadotropin releasing hormone analog (*e.g.*, leuprolide).

Other agents that can be used in combination with the compounds of the disclosure for the treatment of cancer include platinum coordination complexes (*e.g.*, cisplatin, carboblatin), anthracenedione (*e.g.*, mitoxantrone), substituted urea (*e.g.*, hydroxyurea), methyl hydrazine derivative (*e.g.*, procarbazine), and adrenocortical suppressant (*e.g.*, mitotane, aminoglutethimide). Other anti-cancer agents/drugs that can be used in combination with the compounds of the disclosure include, but are not limited to, liver X receptor (LXR) modulators, including LXR agonists and LXR beta-selective agonists; aryl hydrocarbon receptor (AhR) inhibitors; inhibitors of the enzyme poly ADP ribose polymerase (PARP), including olaparib, iniparib, rucaparib, veliparib; inhibitors of vascular endothelial growth factor (VEGF) receptor tyrosine kinases, including cediranib; programmed cell death protein 1 (PD-1) inhibitors, including nivolumab (Bristol-Myers Squibb Co.) and pembrolizumab (Merck & Co., Inc.; MK-3475); MEK inhibitors, including cobimetinib; B-Raf enzyme inhibitors, including vemurafenib; cytotoxic T lymphocyte antigen (CTLA-4) inhibitors, including tremelimumab; programmed death-ligand 1 (PD-L1) inhibitors, including MEDI4736 (AstraZeneca); inhibitors of the Wnt pathway; inhibitors of epidermal growth factor receptor (EGFR) including AZD9291 (AstraZeneca), erlotinib, gefitinib, panitumumab, and cetuximab; adenosine A2A receptor inhibitors; adenosine A2B receptor inhibitors; colony-stimulating factor-1 receptor (CSF1R) inhibitors, including PLX3397 (Plexxikon), and inhibitors of CD73.

The compounds of the disclosure can be used in combination with one or more therapeutic strategies including immune checkpoint inhibitors, including inhibitors of PD-1, PD-L1, and CTLA-4.

The compounds of the disclosure can be used in combination with one or more anti-cancer agents selected from MCL-1 inhibitors, *e.g.*, homoharringtonin (HHT) and omacetaxine; BCL-2 inhibitors, *e.g.*, venetoclax (ABT-199), navitoclax (ABT-263), ABT-737, gossypol (AT-101), apogossypolone (ApoG2) and obatoclax; selective inhibitors of nuclear export (SINEs), *e.g.*, selinexor (KPT-330).

In particular embodiments, the compounds of the disclosure are used in combination with one or more anti-cancer agents selected from methotrexate (Abitrexate®; Folex®; Folex PFS®; Mexate®; Mexate-AQ®); nelarabine (Arranon®); blinatumomab (Blincyto®); rubidomycin hydrochloride or daunorubicin hydrochloride (Cerubidine®); cyclophosphamide (Clafen®; Cytoxan®; Neosar®); clofarabine (Clofarex®; Clolar®); cytarabine (Cytosar-U®;

Tarabine PFS®); dasatinib (Sprycel®); doxorubicin hydrochloride; asparaginase *Erwinia chrysanthemi* (Erwinaze); imatinib mesylate (Gleevec®); ponatinib hydrochloride (Iclusig®); mercaptopurine (Purinethol; Purixan); pegaspargase (Oncaspar®); prednisone; vincristine sulfate (Oncovin®, Vincasar PFS®, Vincrex®); vincristine sulfate liposome (Marqibo®); hyper-CVAD (fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone); arsenic trioxide (Trisenox®); idarubicin hydrochloride (Idamycin®); mitoxantrone hydrochloride; thioguanine (Tabloid®); ADE (cytarabine, daunorubicin, and etoposide); alemtuzumab (Lemtrada®, Campath®); chlorambucil (Ambochlorin®, Amboclorin®, Leukeran®, Linfolizin®); ofatumumab (Arzerra®); bendamustine hydrochloride (Treanda®); fludarabine phosphate (Fludara®); obinutuzumab (Gazyva®); ibrutinib (Imbruvica®); idelalisib (Zydelig®); mechlorethamine hydrochloride (Mustargen®); rituximab (Rituxan®); chlorambucil-prednisone; CVP (cyclophosphamide, vincristine, and prednisone); bosutinib (Bosulif®); busulfan (Busulfex®; Myleran®); omacetaxine mepesuccinate (Synribo®); nilotinib (Tasigna®); Intron® A (recombinant interferon Alfa-2b); DOT1L inhibitors, including EPZ-5676 (Epizyme, Inc.); and inhibitors of bromodomain and extra-terminal motif (BET) proteins (BET inhibitors), including MS417, JQ1, I-BET 762, and I-BET 151 for the treatment of leukemia.

Compounds of the disclosure can be used in combination with one or more other agents or therapies for the treatment of insulin resistance, pre-diabetes, diabetes (*e.g.*, Type 2 diabetes or Type 1 diabetes), and risk of diabetes, including but not limited to insulins and insulin analogues, such as Humulin® (ELi Lilly), Lantus® (Sanofi Aventis), Novolin® (Novo Nordisk), and Exubera® (Pfizer); Avandamet® (metformin HCI and rosiglitazone maleate, GSK); Avandaryl® (glimepiride and rosiglitazone maleate, GSK); Metaglip® (glipizide and metformin HCI, Bristol Myers Squibb); Glucovance® (glyburide and metformin HCI, Bristol Myers Squibb); PPAR gamma agonists, such as Avandia® (rosiglitizone maleate, GSK) and Actos® (pioglitazone hydrochloride, Takeda/Eli Lilly); sulfonylureas, such as Amaryl® (glimepiride, Sanofi Aventis), Diabeta® (glyburide, Sanofi Aventis), Micronase®/Glynase® (glyburide, Pfizer), and Glucotrol®/Glucotrol XL® (glipizide, Pfizer); meglitinides, such as Prandin®/NovoNorm® (repaglinide, Novo Nordisk), Starlix® (nateglinide, Novartis), and Glufast® (mitiglinide, Takeda); biguanides, such as Glucophase®/Glucophase XR® (metformin HCI, Bristol Myers Squibb) and Glumetza® (metformin HCI, Depomed); thiazolidinediones; amylin analogs; GLP-1 analogs; DPP-IV inhibitors such as Januvia® (sitagliptin, Merck) and Galvus® (vildagliptin, Novartis); PTB-1 B inhibitors; protein kinase inhibitors (including AMP-activated protein kinase inhibitors); glucagon antagonists, glycogen synthase kinase-3 beta inhibitors; glucose-6-phoshatase inhibitors; glycogen phosphorylase inhibitors; sodium

glucose co-transporter inhibitors; and alpha-glucosidase inhibitors, such as Glycet® (miglitol, Pfizer); statins, fibrates, and Zetia® (ezetimibe); alpha-blockers; beta-blockers; calcium channel blockers; diuretics; angiotensin converting enzyme (ACE) inhibitors; dual ACE and neutral endopeptidase (NEP) inhibitors; angiotensin-receptor blockers (ARBs); aldosterone synthase inhibitors; aldosterone-receptor antagonists; endothelin receptor antagonists; orlistat; phentermine; sibutramine; Acomplia® (rimonabant); thiazolidinediones (*e.g.*, rosiglitazone, pioglitazone); SGLT 2 inhibitors (*e.g.*, dapagliflozin, remogliflozin etabonate, sergliflozin, canagliflozin, and 1 -chloro-4-(β-D- glucopyranos-1-yl)-2-[4-(('S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene); PPAR-gamma-agonists (*e.g.*, Gl 262570) and antagonists; PPAR-gamma/alpha modulators (*e.g.*, KRP 297); alpha-glucosidase inhibitors (*e.g.*, acarbose, voglibose); DPPIV inhibitors (*e.g.*, Januvia® (sitagliptin), Galvus®/Zomelis® (vildagliptin), Onglyza® (saxagliptin), Nesina®/Vipidia® (alogliptin), and Tradjenta®/Trajenta® (linagliptin)); alpha2-antagonists; glucagon-like protein-1 (GLP-1) receptor agonists and analogues (*e.g.*, exendin-4); amylin; inhibitors of protein tyrosinephosphatase 1; substances that affect deregulated glucose production in the liver, *e.g.*, inhibitors of glucose-6-phosphatase, or fructose-1 ,6- bisphosphatase, glycogen phosphorylase; glucagon receptor antagonists; inhibitors of phosphoenol pyruvate carboxykinase; glycogen synthase kinase and glucokinase activators; lipid lowering agents such as HMG-CoA-reductase inhibitors (*e.g.*, simvastatin, atorvastatin); fibrates (*e.g.*, bezafibrate, fenofibrate), nicotinic acid and the derivatives thereof, PPAR-alpha agonists, PPAR-delta agonists; ACAT inhibitors (*e.g.*, avasimibe); cholesterol absorption inhibitors such as ezetimibe; bile acid-binding substances such as cholestyramine; inhibitors of ileac bile acid transport; HDL-raising compounds such as CETP inhibitors and ABC1 regulators; active substances for treating obesity such as sibutramine and tetrahydrolipostatin; SDRIs; axokine; leptin; leptin mimetics; antagonists of the cannabinoid l receptor; and MCH-1 receptor antagonists; MC4 receptor agonists; NPY5 and NPY2 antagonists; beta3 adrenergic agonists such as SB- 418790 and AD-9677; agonists of the 5HT2c receptor; GABA-receptor antagonists; Na-channel blockers; topiramate; protein-kinase C inhibitors; advanced glycation end product inhibitors; and aldose reductase inhibitors.

Pharmaceutical Formulations, Administration, and Dosage Forms

When employed as pharmaceuticals, the compounds of the disclosure can be administered in the form of a pharmaceutical composition which refers to a combination of a compound of the disclosure, or its pharmaceutically acceptable salt, and at least one pharmaceutically acceptable carrier. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending

upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or intramuscular injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This disclosure also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the disclosure above in combination with one or more pharmaceutically acceptable carriers. In making the compositions of the disclosure, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Compounds or compositions described herein may be administered to a patient using any amount and any route of administration effective for treating or lessening the severity of one or more of the diseases and conditions described herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, disease or disorder, the particular agent, its mode of administration, and the like. Provided compounds are preferably formulated in a particular unit dosage form for ease of administration and uniformity of dosage. The expression "unit dosage form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated.

The therapeutic dosage of the compounds of the present disclosure can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the disclosure in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the disclosure can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration.

EXAMPLES

As depicted in the Examples below, compounds of the disclosure were prepared and isolated according to the following general procedures. It will be appreciated that, although the general methods may depict the synthesis of certain compounds of the present disclosure, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

Abbreviation	Definition
ACN	Acetonitrile
AcOH	Acetic acid
Ac_2O	Acetic anhydride
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
Brettphos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
n-BuOH	*n*-Butanol
t-BuOH	*tert*-Butanol
tBuXphos	[2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl]
Cbz-Cl	Benzyl chloroformate; benzyl chloridocarbonate
CDI	Carbonyldiimadazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane (methylene chloride)
DEE	Diethyl ether
DIBAL-H	Diisobutylaluminium hydride
DIEA (DIPEA)	Diisopropylethylamine
DMA (DMAc)	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane

DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMP	Dess-Martin Periodinane
FA	Formic Acid (HCOOH)
dppf	1,1-bis(Diphenylphosphino)ferrocene
DSC	Differential scanning calorimetry
EDC.HCl	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_3N (TEA)	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour(s)
HATU	1-[bis(Dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzonotrazole
HPLC	High performance liquid chromatography
IPA	Isopropyl alcohol
LAH	Lithium aluminum hydride
LCMS	Liquid chromatography-mass spectrometry
mCPBA	meta-Chloroperoxybenzoic acid
Me	Methyl
MeI	Methyl iodide
MeOH	Methanol
MeOTf	Methyl trifluoromethanesulfonate
MeMgCl	Methylmagnesium chloride
mg	Milligram
min	Minute(s)
mL	Milliliters
mmol	Millimoles
MsCl	Methanesulfonyl chloride
MTBE	*tert*-Butyl methyl ether
MW	Microwave
NCS	*N*-Chlorosuccinamide
NMP	*N*-Methyl-2-pyrrolidone
NOE	Nuclear Overhauser effect
$PdCl_2(dppf).CH_2Cl_2$	[1,1′-bis(Diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd(dppf)Cl_2$	(1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium
Pd-PEPPSI-IHept-Cl	Dichloro[1,3-bis(2,6-di-4-heptylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II)
PhMe	Toluene
i-PrOH	Isopropyl alcohol
ROE	Rotating-frame Overhauser effect
RP	Reverse phase
RT	Room temperature
R_t	Retention time

RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
SFC	Supercritical fluid chromatography
SPhos Pd Gen 2	Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
STAB	Sodium triacetoxyborohydride
Tf_2O	Trifluoromethanesulfonic anhydride
T3P	Propanephosphonic acid anhydride
TBAF	Tetra-n-butylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
pTsCl (TsCl)	4-Toluenesulfonyl chloride
UHP	Urea hydrogen peroxide
UPLC	Ultra-performance liquid chromatography
Xantphos	4,5-bis(Diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexyphosphino-2',4',6'-triisopropyl-1,1'-biphenyl

LCMS

Instrument names: Shimadzu LC2020 Nexera Series; Shimadzu MS2020 N-Series; Agilent 1290 Infinity II series with 1260 MSD.

Method A: Mobile Phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: X Bridge C8 (50 x 4.6) mm, 3.5 µm.

Method B: Mobile Phase A: 0.1% FA in water, mobile phase B: 0.05% FA in ACN; Column: ZORBAX ECLIPSE PLUS C18 (50 x 2.1) mm, 1.8 µm.

Method C: Mobile Phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: Acquity UPLC BEH C18 (50 x 2.1) mm, 1.7 µm.

Method D: Mobile Phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: Phenomenex Kinetex EVO C18 (50 x 3.0) mm, 2.6 µm.

Method E: Mobile Phase A: 0.1% FA in water, mobile phase B: ACN; Column: Acquity BEH C18 (30 x 2.7) mm, 1.7 µm.

Method F: Mobile Phase A: 5 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: Acquity UPLC BEH C18 (50 x 2.1) mm, 1.7 µm.

Method G: Mobile Phase A: 5 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: Phenomenex Kinetex EVO C18 (50 x 3.0) mm, 2.6 µm.

Method H: Mobile Phase A: 0.1% FA in water, mobile phase B: 0.1% FA in ACN; Column: ZORBAX ECLIPSE PLUS C18 (50 x 2.1) mm, 1.8 µm.

Method I: Mobile Phase A: 5 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: X Bridge C8 (50 x 4.6) mm, 3.5 µm.

Method J: Mobile Phase: A: 0.1% TFA in water, mobile phase B: ACN; Column: ZORBAX ECLIPSE PLUS C18 (50 x 2.1) mm, 1.8 µm.

Method K: Mobile Phase A: 0.1% TFA in water, mobile phase B: ACN; Column: X Bridge C8 (50 x 4.6) mm, 3.5 µm.

Method L: Mobile Phase A: 5 mM NH_4HCO_3 in water, mobile phase B: ACN; Column: X Bridge BEH C18 (50 x 2.1) mm, 2.5 µm.

HPLC

Instrument names: Shimadzu LC; Prominence-I series instruments as followed using % with UV detection (Maxplot).

Method A: Mobile Phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Flow Rate: 2.0 mL/min; Column: X-Bridge C8 (150 x 4.6) mm, 5 µm.

Method B: Mobile Phase A: 0.1% TFA in water, mobile phase B: ACN; Flow Rate: 1.0 mL/min; Column: Atlantis column C18 (250 x 4.6) mm, 5 µm.

Method C: Mobile Phase A: 10 mM NH_4OAc in water, mobile phase B: ACN; Flow Rate: 1.5 mL/min; Column: Gemini NX C18 (150 x 4.6) mm, 3 µm.

Method D: Mobile Phase A: 0.1% FA in water, mobile phase B: ACN; Flow Rate: 2.0 mL/min; Column: X-Select CSH C18 (150 x 4.6) mm, 5 µm.

Method E: Mobile Phase A: 0.1% TFA in water, mobile phase B: ACN; Flow Rate: 2.0 mL/min; Column: X-Select CSH C18 (150 x 4.6) mm, 5 µm.

Method F: Mobile Phase A: 10 mM NH_4OAc in water, mobile phase B: ACN; Flow Rate: 1.5 mL/min; Column: X-Bridge C8 (150 x 4.6) mm, 5 µm.

Method G: Mobile Phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Flow Rate: 2.0 mL/min; Column: X-Bridge C18 (150 x 4.6) mm, 5 µm.

Method H: Mobile Phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Flow Rate: 1.2 mL/min; Column: X-Bridge C18 (150 x 4.6) mm, 5 µm.

Method I: Mobile Phase A: 0.1% TFA in water, mobile phase B: ACN; Flow Rate: 1.2 mL/min; Column: Atlantis T3 C18 (150 x 4.6) mm, 3 µm.

Prep HPLC

Instrument names: Agilent Technologies 1260 Infinity II Series LC / 6125 MSD; Shimadzu LC 20 series Prep HPLC/MS2020.

Method A: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Bridge OBD C18 (150 x 19.0) mm, 5 µm.

Method B: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: SHIMPACK GIST C18 (150 x 19.0) mm, 5 µm.

Method C: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Select CSH C18 (250 x 19) mm, 5 µm.

Method D: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: SHIMPACK GIST C18 (250 x 19) mm, 5 µm.

Method E: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Zorbax C18 (150 x 21.2) mm, 5 µm.

Method F: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: YMC Triart C18 (250 x 20) mm, 5 µm.

Method G: Mobile Phase A: 0.1% HCOOH in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Bridge C8 (250 x 19) mm, 5 µm.

Method H: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Phenomenex gemini-nx (250 x 21.2) mm, 5 µm.

Method I: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: YMC Triart C18 (250 x 20) mm, 5 µm.

Method J: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 10.0 mL/min; Column: X-Bridge C8 (250 x 19) mm, 5 µm.

Method K: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: X-Select CSH C18 (250 x 19) mm, 5 µm.

Method L: Mobile phase A: 10 mM NH_4HCO_3 in water, mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Phenomenex gemini-nx (250 x 21.2 mm) 5 µm.

Method M: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 10.0 mL/min; Column: YMC Triart C18 (250 x 20) mm, 5 µm.

Method N: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: X-Select CSH C18 (250 x 19) mm, 5 µm.

Method O: Mobile Phase A: 0.1% TFA in water; mobile phase B: ACN, Flow Rate: 12.0 mL/min; Column: YMC ACTUS C18 (250 x 20) mm, 5 µm.

Method P: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: X-Bridge OBD C18 (150 x 19) mm, 5 µm.

Method Q: Mobile Phase A: 0.1% FA in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Shimpack GIST C18 (150 x 19) mm, 5 µm.

Method R: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 10.0 mL/min; Column: X-Bridge OBD C18 (250 x 19) mm, 5 µm.

Method S: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 10.0 mL/min; Column: X-Bridge OBD C18 (150 x 19) mm, 5 µm.

Method T: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: Shimpack GIST C18 (250 x 19) mm, 5 µm.

Method U: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: X-Select C18 (150 x 19) mm, 5 µm.

Method V: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Select C18 (150 x 19) mm, 5 µm.

Method W: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Bridge C8 (250 x 19)mm, 5 µm.

Method X: Mobile Phase A: 0.1% TFA in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Select CSH C18 (150 x 19) mm, 5 µm.

Method Y: Mobile Phase A: 0.1% FA in water, mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Select CSH C8 (150 x 19) mm, 5 µm.

Method Z: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: X-Bridge C8 (250 x 19) mm, 5 µm.

Method AA: Mobile Phase A: 0.1% TFA in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Sunfire C18 (150 x 19) mm, 5 µm.

Method AB: Mobile Phase A: 0.1% FA in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: X-Select C18 (250 x 19) mm, 5 µm.

Method AC: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; SHIMPACK SCEPTER C18 (150 x 19) mm, 5 µm.

Method AD: Mobile Phase A: 10 mM NH_4HCO_3 in water mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Bridge OBD C18 (250 x 19) mm, 5 µm.

Method AE: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Zorbax C18 (50 x 21.2) mm, 5 µm.

Method AF: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: X-Bridge C8 (150 x 19) mm, 5 µm.

Method AG: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 10.0 mL/min; Column: X-Bridge C8 (150 x 19) mm, 5 µm.

Method AH: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Bridge C8 (150 x 19) mm, 5 µm.

Method AI: Mobile Phase A: 10 mM NH_4OAc in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Shimpack GIST C18 (150 x 19) mm, 5 µm.

Method AJ: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: YMC C8 (250 x 20) mm, 5 µm.

Method AK: Mobile Phase A: 0.1% FA in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: Shimpack GIST C18 (250 x 19.0) mm, 5 µm.

Method AL: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 12.0 mL/min; Column: YMC C18 (250 x 20) mm, 5 µm.

Method AM: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: SHIMPACK GIST C18 (150 x 19) mm, 5 µm.

Method AN: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Bridge 5u C8 (250 x 21.1) mm, 5 µm.

Method AO: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Select CSH C18 (150 x 19) mm, 5 µm.

Method AP: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: Zorbax C18 (50 x 21.2) mm, 5 µm.

Method AQ: Mobile Phase A: 0.1% FA in water, mobile phase B: ACN; Flow Rate: 15.0 mL/min; Column: X-Select CSH C18 (250 x 19) mm, 5 µm.

Method AR: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: X-Select CSH C18 (150 x 19) mm, 5 µm.

Method AS: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 18.0 mL/min; Column: X-Timate C18 (250 x 21.2) mm, 5 µm.

Method AR: Mobile Phase A: 10 mM NH_4HCO_3 in water; mobile phase B: ACN; Flow Rate: 13.0 mL/min; Column: X-Timate C18 (250 x 21.2) mm, 5 µm

Achiral Prep SFC

Instrument names: PIC-SFC-175; PIC-SFC-400

Method A: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (85:15); Flow Rate: 100 mL/min; % Co-Solvent: 15%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method B: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (65:35); Flow Rate: 120 mL/min; % Co-Solvent: 35%; Column: DIOL (250 x 30) mm, 5 µm.

Method C: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 100 mL/min; % Co-Solvent: 40%; Column: DIOL (250 x 30) mm, 5 µm.

Method D: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH (90:10); Flow Rate: 100 mL/min; % Co-Solvent: 10%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method E: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (90:10); Flow Rate: 120 mL/min; % Co-Solvent: 10%; Co-Solvent: 10%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method F: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 25%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method G: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 120 mL/min; % Co-Solvent: 30%; Column: DIOL (250 x 30) mm, 5 µm.

Method H: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (80:20); Flow Rate: 120 mL/min; % Co-Solvent: 20%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method I: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 25%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method J: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 100 mL/min; % Co-Solvent: 35%; Column: Ethyl pyridine (250 x 30) mm, 5 µm .

Method K: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA: ACN (60:30); Flow Rate: 100 mL/min; % Co-Solvent: 30%; Column: DIOL (250 x 30) mm, 5 µm.

Method L: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 120 mL/min; % Co-Solvent: 25%; Column: DIOL (250 x 30) mm, 5 µm.

Method M: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH: ACN (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 30%; Column: DIOL (250 x 30) mm, 5 µm.

Method N: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (85:15); Flow Rate: 120 mL/min; % Co-Solvent: 15%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method O: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 120 mL/min; % Co-Solvent: 30%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method P: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH (85:15); Flow Rate: 100 mL/min; % Co-Solvent: 15%; Column: DIOL (250 x 30) mm, 5 µm.

Method Q: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (80:20); Flow Rate: 120 mL/min; % Co-Solvent: 20%; Column: DIOL (250 x 30) mm, 5 µm.

Method R: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 25%; Column: DIOL (250 x 30) mm, 5 µm.

Method S: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH:ACN (1:1) (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 25%; Column: 4-Ethyl pyridine (250 x 30) mm, 5 µm.

Method T: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 100 mL/min; % Co-Solvent: 30%; Column: DIOL (250 x 30) mm, 5 µm.

Chiral SFC

Instrument names: Shimadzu Nexera UC SFC Analytical; PIC- SFC Analytical-10

Method A: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: LUX-C4 (250 x 4.6) mm, 5 µm.

Method B: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose B (250 x 4.6) mm, 5 µm.

Method C: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method D: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: LUX-A1 (250 x 4.6) mm, 5 µm.

Method E: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose B (250 x 4.6) mm, 5 µm.

Method F: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 5.0 mL/min; % Co-Solvent: 30%; Column: I-Cellulose B (250 x 4.6) mm, 5 μm.

Method G: Mobile Phase A: CO2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 4.0 mL/min; % Co-Solvent: 30%; Column: I-Cellulose B (250 x 4.6) mm, 5 μm.

Method H: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 μm.

Method I: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: LUX-C4 (250 x 4.6) mm, 5 μm.

Method J: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose Z (250 x 4.6) mm, 5 μm.

Method K: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 μm.

Method L: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: CHIRALPAK-IH (250 x 4.6) mm, 5 μm.

Method M: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 5.0 mL/min; % Co-Solvent: 25%; Column: I Amylose A (250 x 4.6) mm, 5 μm.

Method N: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose J (250 x 4.6) mm, 5 μm.

Method O: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 μm.

Method P: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: I Amylose A (250 x 4.6) mm, 5 μm.

Method Q: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (50:50); Flow Rate: 5.0 mL/min; % Co-Solvent: 50%; Column: CHIRALCEL-OX-H (250 x 4.6) mm, 5 μm.

Method R: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH: IPA (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: CHIRALPAK-AD-H (250 x 4.6) mm, 5 μm.

Method S: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 5.0 mL/min; % Co-Solvent: 30%; Column: I Amylose-A (250 x 4.6) mm, 5 μm.

Method T: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 5.0 mL/min; % Co-Solvent: 30%; Column: CHIRALPAK-AS-H (250 x 4.6) mm, 5 μm.

Method U: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 μm.

Method V: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: I Amylose A (250 x 4.6) mm, 5 μm.

Method W: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: I Amylose A (250 x 4.6) mm, 5 μm.

Method X: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: CHIRALPAK-IK (250 x 4.6) mm, 5 μm.

Method Y: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 4.0 mL/min; % Co-Solvent: 30%; Column: LUX-I-A3 (250 x 4.6) mm, 5 μm.

Method Z: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: I-Cellulose Z (250 x 4.6) mm, 5 μm.

Method AA: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: LUX-A1 (250 x 4.6) mm, 5 μm.

Method AB: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 5.0 mL/min; % Co-Solvent: 35%; Column: I-Cellulose B (250 x 4.6) mm, 5 μm.

Method AC: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: I-Cellulose B (250 x 4.6) mm, 5 μm.

Method AD: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN:MeOH (1:1)] (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AE: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN:MeOH (1:1)] (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AF: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AG: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AH: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 4.0 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AI: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: LUX-Amylose-1 (250 x 4.6) mm, 5 µm.

Method AJ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AK: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 4.0 mL/min; % Co-Solvent: 35%; Column: I-Cellulose B (250 x 4.6) mm, 5 µm.

Method AL: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AM: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (80:20); Flow Rate: 4.0 mL/min; % Co-Solvent: 20%; Column: I-Amylose A (250 x 4.6) mm, 5 µm.

Method AN: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; LUX Amylose-1 (250 x 4.6) mm, 5 µm.

Method AO: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: CHIRALPAK-AS-H (250 x 4.6) mm, 5 µm.

Method AP: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: I-Cellulose-AS-H (250 x 4.6) mm, 5 µm.

Method AQ: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in IPA (70:30); Flow Rate: 5.0 mL/min; % Co-Solvent: 30%; Column: I-Cellulose B (250 x 4.6) mm, 5 µm.

Method AR: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in [ACN: MeOH (1:1)] (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: LUX-I-Amylose-3 (250 x 4.6) mm, 5 µm.

Method AS: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: CHIRALPAK-IG (250 x 4.6) mm, 5 µm.

Method AT: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 µm.

Method AU: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (85:15); Flow Rate: 4.0 mL/min; % Co-Solvent: 15%; Column: LUX-A1 (250 x 4.6) mm, 5 µm.

Method AV: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AW: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: I Amylose A (250 x 4.6) mm, 5 µm.

Method AX: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 4.0 mL/min; % Co-Solvent: 35%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AY: Mobile Phase A: CO2; Co-solvent - 0.5% Isopropylamine in [ACN:MeOH (1:1)] (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: C Cellulose B (250 x 4.6) mm, 5 µm.

Method AZ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAA: Mobile Phase A: CO2; Co-solvent - 0.5% Isopropylamine in [IPA:ACN (1:1)] (60:40); Flow Rate: 5.0 mL/min; % Co-Solvent: 40%; Column: CHIRALPAK-IK (250 x 4.6) mm, 5 µm.

Method AAB: Mobile Phase A: CO2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 4.0 mL/min; % Co-Solvent: 30%; Column: C Cellulose B (250 x 4.6) mm, 5 µm.

Method AAC: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: CHIRALPAK-IK (250 x 4.6) mm, 5 µm.

Method AAD: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: IPA (1:1)] (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AAE: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in ACN:MeOH (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AAF: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 4.0 mL/min; % Co-Solvent: 35%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 µm.

Method AAG: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 5.0 mL/min; % Co-Solvent: 45%; Column: CHIRALPAK-IK (250 x 4.6) mm, 5 µm.

Method AAH: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: I Cellulose B (250 x 4.6) mm, 5 µm.

Method AAI: Mobile Phase A: CO2; Co-solvent - 0.5% Isopropylamine in [IPA:ACN (1:1)] (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: I Cellulose B (250 x 4.6) mm, 5 µm.

Method AAJ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (75:25); Flow Rate: 4.0 mL/min; % Co-Solvent: 25%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 µm.

Method AAK: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: LUX-C4 (250 x 4.6) mm, 5 µm.

Method AAL: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (70:30); Flow Rate: 4.0 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAM: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAN: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN:MeOH (1:1)] (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAO: Mobile Phase A: CO2; Co-solvent - 0.5% diethylamine in EtOH (80:20); Flow Rate: 4.0 mL/min; % Co-Solvent: 20%; Column: C Cellulose B (250 x 4.6) mm, 5 µm.

Method AAP: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 5.0 mL/min; % Co-Solvent: 30%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 µm.

Method AAQ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (65:35); Flow Rate: 4.0 mL/min; % Co-Solvent: 35%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAR: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 4.0 mL/min; % Co-Solvent: 40%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AAS: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: LUX-I-Amylose3 (250 x 4.6) mm, 5 µm.

Method AAT: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN:MeOH (1:1)] (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: LUX-Cellulose-4 (250 x 4.6) mm, 5 µm.

Method AAU: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 5.0 mL/min; % Co-Solvent: 25%; Column: I-Cellulose B (250 x 4.6) mm, 5 µm.

Method AAV: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 5.0 mL/min; % Co-Solvent: 30%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 µm.

Method AAW: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [IPA: ACN (1:1) (55:45)]; Flow Rate: 4 mL/min; % Co-Solvent: 45%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAX: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (85:15); Flow Rate: 4.0 mL/min; % Co-Solvent: 15%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAY: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (55:45); Flow Rate: 4.0 mL/min; % Co-Solvent: 45%; Column: I-Cellulose B (250 x 4.6) mm, 5 µm.

Method AAZ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (50:50); Flow Rate: 5.0 mL/min; % Co-Solvent: 45%; Column: Whelk-(R,R) (250 x 4.6) mm, 5 µm.

Method AAAA: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1) (55:45)]; Flow Rate: 4 mL/min; % Co-Solvent: 45%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAAB: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 5.0 mL/min; % Co-Solvent: 35%; Column: I Amylose A (250 x 4.6) mm, 5 µm.

Method AAAC: Mobile Phase A: CO_2; Co-solvent - Methanol: Acetonitrile (1:1) (65:35); Flow Rate: 4 mL/min; % Co-Solvent: 35%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAAD: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 4.0 mL/min; % Co-Solvent: 30%; Column: I Amylose-A (250 x 4.6) mm, 5 µm.

Method AAAE: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: LUX-C4 (250 x 4.6) mm, 5 µm.

Method AAAF: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (45:55); Flow Rate: 4.0 mL/min; % Co-Solvent: 55%; Column: I-Cellulose Z (250 x 4.6) mm, 5 µm.

Method AAAG: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (50:50); Flow Rate: 4.0 mL/min; % Co-Solvent: 50%; Column: I-Cellulose Z (250 x 4.6) mm, 5 μm.

Chiral HPLC

Method A: Mobile Phase A: ACN:MEOH:DEA (85/15/0.1) Flow Rate: 1.5 mL/min; Column: CHIRALPAK IK (250 X 4.6) mm, 5 μm.

Chiral Prep SFC

Method A: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (58:42); Flow Rate: 120 mL/min; % Co-Solvent: 42%; Column: LUX C4 (250 x 30) mm, 5 μm.

Method B: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (58:42); Flow Rate: 120 mL/min; % Co-Solvent: 42%; Column: LUX C4 (250 x 30) mm, 5 μm.

Method C: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 100 mL/min; % Co-Solvent: 40%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method D: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 50 mL/min; % Co-Solvent: 30%; Column: LUX-A1 (250 x 20) mm, 5 μm.

Method E: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 100 mL/min; % Co-Solvent: 40%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method F: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 100 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method G: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in IPA (50:50); Flow Rate: 50 mL/min; % Co-Solvent: 50%; Column: LUX A3 (250 x 20) mm, 5 μm.

Method H: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (55:45); Flow Rate: 100 mL/min; % Co-Solvent: 45%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method I: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in IPA (80:20); Flow Rate: 50 mL/min; % Co-Solvent: 20%; Column: LUX A3 (250 x 30) mm, 5 μm.

Method J: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 120 mL/min; % Co-Solvent: 25%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method K: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 120 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method L: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [IPA: ACN (1:1) (50:50)]; Flow Rate: 100 mL/min; % Co-Solvent: 50%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method M: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (80:20);); Flow Rate: 100 mL/min; % Co-Solvent: 20%; Column: LUX C4 (250 x 30) mm, 5 μm.

Method N: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 120 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 21) mm, 5 μm.

Method O: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (85:15); Flow Rate: 60 mL/min; % Co-Solvent: 15%; Column: I Amylose A (250 x 30) mm, 5 μm.

Method P: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (65:35); Flow Rate: 100 mL/min; % Co-Solvent: 35%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method Q: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [MeOH: ACN (1:1) (75:25)]; Flow Rate: 120 mL/min; % Co-Solvent: 25%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method R Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 25%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method S Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [IPA: ACN (1:1) (55:45)]; Flow Rate: 100 mL/min; % Co-Solvent: 45%; Column: Chiral Pak-IK (250 x 30) mm, 5 μm.

Method T: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 60 mL/min; % Co-Solvent: 30%; Column: C-Cellulose B (250 x 21.2) mm, 5 μm.

Method U: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH (60:40); Flow Rate: 60 mL/min; % Co-Solvent: 40%; Column: RR WHELK (250 x 21) mm, 5 μm

Method V: Mobile Phase A: CO2; Co-solvent - 0.5% Isopropylamine in IPA (65:35); Flow Rate: 100 mL/min; % Co-Solvent: 35%; Column: I Cellulose J (250 x 30) mm, 5 µm.

Method W: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in [IPA: ACN (1:1) (70:30)]; Flow Rate: 100 mL/min; % Co-Solvent: 30%; Column: LUX A3 (250 x 30) mm, 5 µm.

Method X: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 60 mL/min; % Co-Solvent: 30%; Column: LUX C2 (250 x 20) mm, 5 µm.

Method Y: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN:MeOH (60:40); (50:50)] Flow Rate: 50 mL/min; % Co-Solvent: 50%; Column: LUX A3 (250 x 21) mm, 5 µm.

Method Z: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (70:30); Flow Rate: 60 mL/min; % Co-Solvent: 30%; Column: Lux C2 (250 x 20) mm, 5 µm.

Method AA: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (80:20); Flow Rate: 110 mL/min; % Co-Solvent: 20%; Column: Chiral Pak-ASH (250 x 30) mm, 5 µm.

Method AB: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA: ACN (1:1) (60:40); Flow Rate: 100 mL/min; % Co-Solvent: 40%; Column: I-Cellulose B (250 x 30)mm, 5µm.

Method AC: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in IPA (60:40); Flow Rate: 60 mL/min; % Co-Solvent: 50%; Column: LUX A3 (250 x 20) mm, 5 µm.

Method AD: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (55:45); Flow Rate: 100 mL/min; % Co-Solvent: 45%; Column: Chiral Pak-IK (250 x 30) mm, 5 µm.

Method AE: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (1:1)] (70:30); Flow Rate: 100.0 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 30) mm, 5 µm.

Method AF: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (50:50); Flow Rate: 100 mL/min; % Co-Solvent: 50%; Column: I-Cellulose Z (250 x 30) mm, 5 µm.

Method AG: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [MeOH: ACN (1:1) (70:30)]; Flow Rate: 120 mL/min; % Co-Solvent: 30%; Column: I-Cellulose Z (250 x 30) mm, 5 µm.

Method AH: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in MeOH (50:50); Flow Rate: 50 mL/min; % Co-Solvent: 50%; Column: LUX A3 (250 x 20) mm, 5 µm.

Method AI: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (85:15); Flow Rate: 100 mL/min; % Co-Solvent: 15%; Column: LUX A3 (250 x 20) mm, 5 µm

Method AJ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 120 mL/min; % Co-Solvent: 25%; Column: Chiral Pak-AS-H (250 x 30) mm, 5 µm.

Method AK: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in [ACN: MeOH (3:2)] (75:25); Flow Rate: 120 mL/min; % Co-Solvent: 25%; Column: RR WHELK (250 x 30) mm, 5 µm.

Method AL: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (55:45); Flow Rate: 100 mL/min; % Co-Solvent: 45%; Column: LUX I Amylose 3 (250 x 30) mm, 5 µm.

Method AM: Mobile Phase A: CO_2: Co-solvent - 0.5% Isopropylamine in MeOH: CAN (1:1) (55:45); Flow Rate: 60 mL/min; % Co-Solvent: 45%; Column: LUX C2 (250 x 20) mm, 5 µm.

Method AN: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA: ACN (1:1) (70:30); Flow Rate: 120 mL/min; % Co-Solvent: 30%; Column: I-Cellulose B (250 x 30)mm, 5µm.

Method AO: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [MeOH:ACN (1:1)] (70:30); Flow Rate: 70 mL/min; % Co-Solvent: 30%; Column: LUX C4 (250 x 20) mm, 5 µm.

Method AP: Mobile Phase A: CO_2: Co-solvent 0.5% Isopropylamine in [MeOH:ACN (1:1)] (70:30; Flow Rate: 60 mL/min; % Co-Solvent: 30%; Column: LUX A3 (250 x 20) mm, 5 µm.

Method AQ: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (75:25); Flow Rate: 120 mL/min; % Co-Solvent: 40%; Column: I-Cellulose B (250 x 30)mm, 5µm.

Method AR: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (60:40); Flow Rate: 60 mL/min; % Co-Solvent: 40%; Column: Chiral Pak-ASH (250 x 30) mm, 5 µm.

Method AS: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (75:25); Flow Rate: 100 mL/min; % Co-Solvent: 25%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method AT: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in [MeOH: ACN (1:1) (60:40)]; Flow Rate: 120 mL/min; % Co-Solvent: 40%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method AU: Mobile Phase A: CO_2; Co-solvent - Methanol: Acetonitrile(1:1) (65:35); Flow Rate: 100 mL/min; % Co-Solvent: 35%; Column: I-Cellulose Z (250 x 30) mm, 5 μm.

Method AV: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in IPA (70:30); Flow Rate: 60 mL/min; % Co-Solvent: 30%; Column: I Amylose A (250 x 20) mm, 5 μm.

Method AW: Mobile Phase A: CO_2; Co-solvent - 0.5% Isopropylamine in MeOH (50:50); Flow Rate: 60 mL/min; % Co-Solvent: 50%; Column: LUX-C4 (250 x 21) mm, 5 μm.

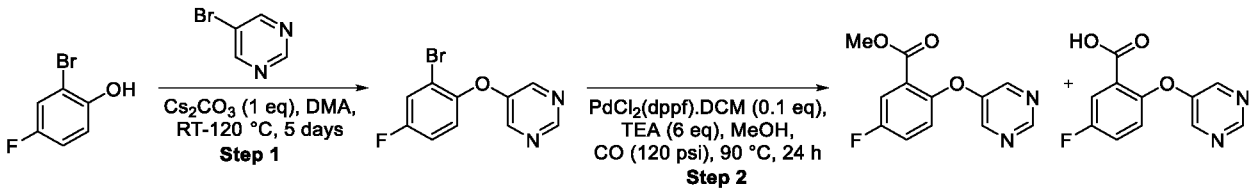
Chiral Prep HPLC

Method A: Mobile Phase A: ACN:MEOH:DEA (85/15/0.1); Flow Rate: 40 mL/min; Column: CHIRALPAK IK (250 X 30) mm, 5 μm.

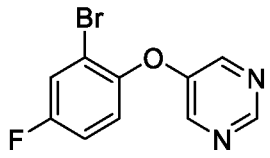
Method B: Mobile Phase: n-Hexane/EtOH/MeOH (85/05/10); Flow Rate: 20 mL/min; Column: CHIRALCEL OD-H (250 x 30) mm, 5 μm.

Synthesis of Intermediates

Intermediate 1. Methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate



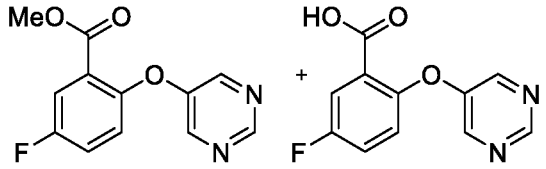
Step 1. 5-(2-Bromo-4-fluorophenoxy)pyrimidine



Step 1 was performed following the same procedure in two batches, a 450 g batch and a 200 g batch.

In a dried, 10 L four neck round bottom flask under nitrogen atmosphere, 2-bromo-4-fluorophenol (450 g, 2356 mmol) was dissolved in DMA (2.5 L) at RT. To this reaction mixture, Cs_2CO_3 (768 g, 2356 mmol) and 5-bromopyrimidine (375 g, 2356 mmol) were added at RT. The reaction was heated at 120 °C for 5 days. The reaction progress was monitored by LCMS and TLC (10% EtOAc in hexane). The reaction mixture from both batches (450 g and 200 g) were combined, quenched with water (3 L), and extracted with MTBE (2 x 5 L). The combined organic layer was washed with water (2 L) and brine solution (2 L), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica-gel column chromatography using EtOAc in hexane (product eluted at 4% EtOAc in hexane) to obtain 5-(2-bromo-4-fluorophenoxy)pyrimidine (380 g, 38.9% combined yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.57 (s, 2H), 7.81 (dd, J = 2.9, 8.2 Hz, 1H), 7.46 - 7.33 (m, 2H); LCMS (Method H): Rt = 1.79 min, m/z = 269.2 $[M+H]^+$, 78.45%.

Step 2. Methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate and 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid



Step 2 was performed following the same procedure in sixteen batches, a 21.5 g batch, and 15 x 20 g batches.

In a 300 mL stainless steel mini clave, 5-(2-bromo-4-fluorophenoxy)pyrimidine (20 g, 74.3 mmol) was added in MeOH (150 mL), and the solution was degassed with argon for 30 min. TEA (61.0 mL, 446 mmol) was added to this solution, and the reaction mixture was degassed for another 5 min. To the above solution, $PdCl_2$(dppf)-CH_2Cl_2adduct (6.07 g, 7.43 mmol) was added, and the reaction was stirred under 120 psi carbon monoxide gas atmosphere (Caution: toxic gas) at 90 °C for 24 h. The reaction was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with methanol (150 mL). The filtrate was concentrated under reduced pressure to obtain crude products (22 g). Similarly, all sixteen batches (21.5 g batch and 15 x 20 g batches) were filtered, and the filtrate was concentrated under reduced pressure to obtain crude product separately. The combined crude material (320 g) from sixteen batches were collected and dissolved in EtOAc (2 L). To this solution, 10% sodium bicarbonate (2 L) solution was added, and the mixture was extracted with EtOAc (2 x 2 L). The combined organic layer was dried

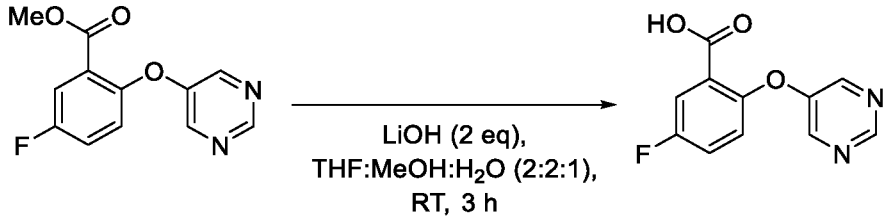
over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane as an eluent (product eluted at 15-20 % EtOAc in hexane) to obtain pure methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (198 g, 62.2% combined yield) as a solid. Further, the aqueous layer was acidified with conc. HCl (pH ~2), and the precipitate was filtered and dried under vacuum to obtain crude 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (25 g, 7.99 % yield) as a solid. This material was used without further purification.

Methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.50 (s, 2H), 7.74 (dd, J = 3.1, 8.8 Hz, 1H), 7.60 (ddd, J = 3.3, 7.9, 9.0 Hz, 1H), 7.44 (dd, J = 4.6, 9.0 Hz, 1H), 3.74 (s, 3H); LCMS (Method D): Rt = 1.65 min, m/z = 249.1 $[M+H]^+$, 92.80%.

5-Fluoro-2-(pyrimidin-5-yloxy)benzoic acid: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (br s, 1H), 8.92 (s, 1H), 8.47 (s, 2H), 7.70 (dd, J = 3.3, 8.9 Hz, 1H), 7.55 (ddd, J = 3.3, 7.9, 8.9 Hz, 1H), 7.40 (dd, J = 4.6, 9.0 Hz, 1H); LCMS (Method H): Rt = 1.26 min, m/z = 235.2 $[M+H]^+$, 74.16%.

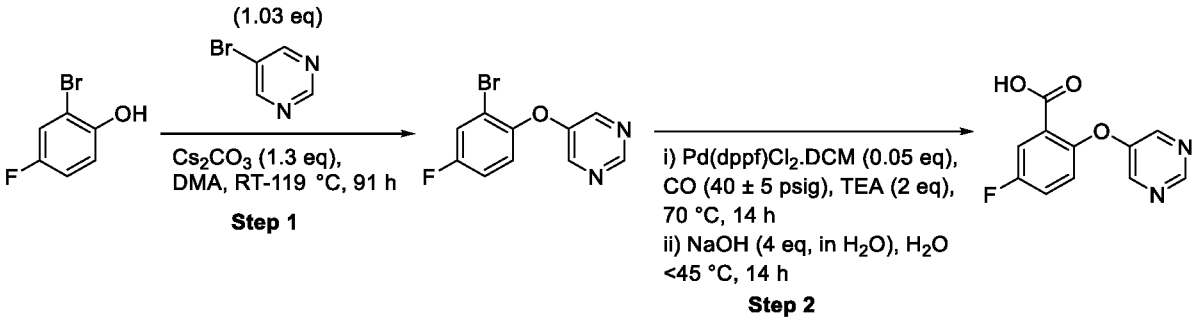
Intermediate 2. 5-Fluoro-2-(pyrimidin-5-yloxy)benzoic acid

First Procedure:

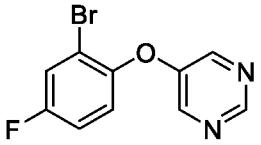


In a 1000 mL 3 neck round bottom flask under nitrogen atmosphere, methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (32 g, 129 mmol) was added in a mixture of MeOH (125 mL), THF (125 mL), and water (62.5 mL). To this solution, LiOH.H_2O (10.82 g, 258 mmol) was added, and the reaction was stirred at RT for 3 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and the aqueous layer was acidified with 1.5 N HCl (pH ~6). The solid was filtered, and the solid was transferred to a round bottom flask and co-distilled with toluene under reduced pressure to obtain 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (29.485 g, 93% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.42 (br s, 1H), 8.92 (s, 1H), 8.47 (s, 2H), 7.70 (dd, J = 3.2, 8.8 Hz, 1H), 7.56 (ddd, J = 3.3, 7.9, 9.0 Hz, 1H), 7.40 (dd, J = 4.6, 9.0 Hz, 1H); LCMS (Method B): Rt = 1.66 min, m/z = 235 $[M+H]^+$; 95.07%.

Second Procedure:



Step 1. 5-(2-Bromo-4-fluorophenoxy)pyrimidine

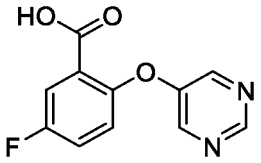


Step 1 was performed in three batches, an 8.00 kg batch (4.00 kg and 4.00 kg from in one reactor and divided into two reactors for workup) and a 3.00 kg batch.

In a 100-L, cylindrical reactor, 2-bromo-4-fluorophenol (8.00 kg, 41.9 mol, 1.00 equiv), 5-bromopyrimidine (6.86 kg, 43.1 mol, 1.03 equiv), cesium carbonate (17.7 kg, 54.5 mol, 1.3 equiv), and DMAc (48 L, 6 vol) were charged. The batch was heated to 119 °C over 9 h and held at temperature for 82 h. The batches were then cooled to 34 °C and an IPC sample was taken, which indicated 82.2% conversion by NMR from the phenol. The internal temperature of the batch was adjusted to 25 °C and the batch was split into two 100-L reactors. To each batch, MTBE (10.6 L, 2.66 vol) and deionized water (48 L, 12 vol), were added and agitated 15 min. The extraction of the resulting aqueous phase was repeated on each batch 5 times with MTBE (5 × 10.6 L, 5 × 2.66 vol for each). The MTBE extracts were combined and washed sequentially with 2 N sodium hydroxide (8 L, 2 vol, 50% NaOH), 0.5 M citric acid (4 L, 1 vol, solid), and finally by 5 wt % sodium bicarbonate (4 L, 1 vol). The MTBE solutions were combined and concentrated via rotary evaporation (bath temperature 55 °C). The residue from the combined batch was then stored in a carboy prior to wiped film evaporation purification. Similarly, a 3.00 kg batch was completed, and the crude oil was stored in a carboy at ambient temperature until purification (3.50 kg). A 4" Pope wiped-film evaporator (WFE) was used to purify 8.17 kg crude 5-(2-bromo-4- fluorophenoxy)pyrimidine through multiple passes. The conditions for WFE distillation first pass were as follows: vacuum 10–12 Torr (empty), wiper speed 328–333 rpm, jacket temperature 160 °C, condenser temperature 85 C, addition rate ~4 mL/min. The conditions for WFE distillation second pass were as follows: vacuum 0.8 Torr (empty), wiper speed 320–330 rpm, jacket

temperature 150 C, condenser temperature 50 C, addition rate ~10 mL/min. A third pass was completed to re-pass pot fractions that contained large amounts of products. The conditions for WFE distillation third pass were as follows: vacuum 0.8 Torr (empty), wiper speed 320–330 rpm, jacket temperature 130 C, condenser temperature 50 C, addition rate ~15 mL/min. After the third pass, the product spontaneously crystallized upon cooling. All the material was collected and combined in several jars with the purified material (6.58 kg, 43% yield combined, 95.9% AUC 91.2 wt % 1H qNMR).

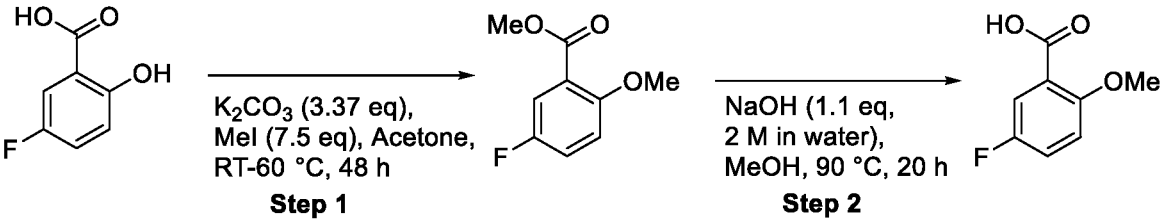
Step 2. 3.5-Fluoro-2-(pyrimidin-5-yloxy)benzoic acid



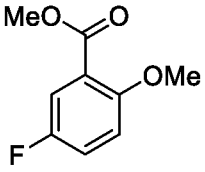
A 22-gal, jacketed, stainless steel pressure vessel was charged with [1,1'-bis(diphenylphosphino) ferrocene]dichloro-palladium(II) dichloromethane adduct ($Pd(dppf)Cl_2$ DCM complex, 0.989 kg, 1.21 moles, 0.05 equiv), 5-(2-bromo-4-fluorophenoxy)pyrimidine (6.52 kg, 24.2 moles, 1.00 equiv), triethylamine (4.93 kg, 48.4 moles, 2.00 equiv), and methanol (32.6 L, 5 vol). The reactor was purged with nitrogen (3 times up to 60 psig of nitrogen pressure) and then with carbon monoxide gas [3 times up to 50 psig of carbon monoxide]. The reactor internal temperature was adjusted to 70 ± 5 °C over 1 h and the internal pressure was adjusted to 40 ± 5 psig with carbon monoxide gas. The batch was stirred at 70 ± 5 C for 13 h, cooled to 25 C, and purged with nitrogen three times with 50 psig pressure. The batch was filtered over a Celite® pad to remove the palladium catalyst, which was rinsed with MeOH (6.5 L, 1 vol). The solution containing methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate was transferred to a100-L, jacketed, glass reactor and diluted with water (13 L, 2 vol). 50 wt % sodium hydroxide aqueous solution (7.8 kg, 96.9 moles, 4 equiv) was added keeping the batch internal temperature <45 C (max temperature 42.4 C). The batch was stirred for 14 h then concentrated under reduced pressure (28.5 in Hg, 42 o C) to 4 vol (24 L). The batch was diluted with water (34 L, 7 vol), cooled to 25 C, and filtered through a Celite® pad to remove the remaining catalyst. The pad was washed with water (6.5 L, 1 vol). The batch was extracted with MTBE (13 L, 2 vol) two times for 30 min each time. The batch was acidified to pH ~2 using 6 M hydrochloric acid (about 13 L, 2.3 vol; conc. HCl), maintaining an internal batch temperature of 20 C. Once the acid addition was complete, the batch was stirred for 20 h, then filtered over a polypropylene cloth using a filter/dryer. The filter cake was washed three times with water (3 × 13 L, 3 × 2 vol)

and dried under a stream of nitrogen at 40–45 C over five days until the water level was 0.3 wt % by KF analysis. The product was isolated in 98% yield (5.58 kg, 98.8% AUC).

Intermediate 3. 5-Fluoro-2-methoxybenzoic acid

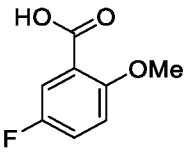


Step 1. Methyl 5-fluoro-2-methoxybenzoate



To a dried, 25 L four neck round bottom flask under nitrogen atmosphere, 5-fluoro-2-hydroxybenzoic acid (800 g, 5125 mmol) was added in acetone (7 L). K_2CO_3 (2387 g, 17271 mmol) was added to this solution, followed by the dropwise addition of MeI (2394 mL, 38437 mmol) at RT. The resulting reaction was heated at 60 °C for 48 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was filtered and concentrated under reduced pressure. The residue was diluted with water (4000 mL) and extracted with EtOAc (3 x 2000 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain methyl 5-fluoro-2-methoxybenzoate (930 g, 97% yield) as a gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 – 7.37 (m, 2H), 7.18 (dd, J = 4.4, 9.1 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H); LCMS (Method H): Rt = 1.70 min, m/z = 185.2 $[M+H]^+$; HPLC (Method A): Rt = 5.05 min, 98.07%.

Step 2. 5-Fluoro-2-methoxybenzoic acid

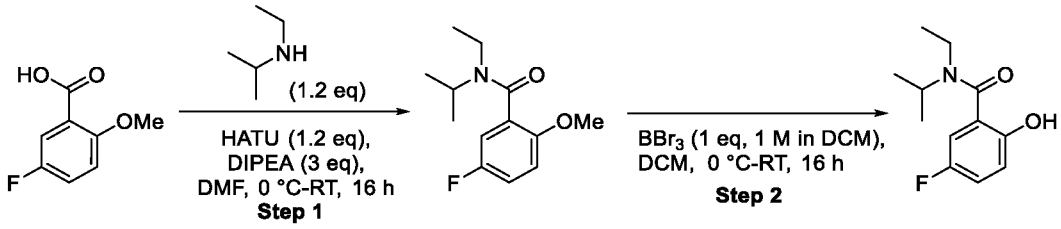


In a 25 L four neck round bottom flask, methyl 5-fluoro-2-methoxybenzoate (1.45 kg, 7.87 mol) was added in MeOH (5 L). To this solution, NaOH (4330 mL, 8.66 mol, 2 M in H_2O) was added at RT, and the reaction was stirred at 90 °C for 20 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was concentrated, diluted with water (5 L), and acidified to pH 2 with 1.5 N HCl (5 L). The resulting solid compound was filtered, washed with water (5 L), and dried under reduced pressure to obtain 5-fluoro-2-methoxybenzoic acid (1.2 kg, 89% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85

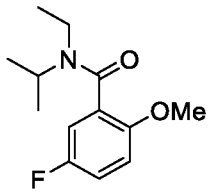
(br s, 1H), 7.41 (dd, J = 3.3, 8.8 Hz, 1H), 7.35 (ddd, J = 3.3, 8.1, 9.1 Hz, 1H), 7.14 (dd, J = 4.3, 9.1 Hz, 1H), 3.80 (s, 3H); LCMS (Method H): Rt = 1.31 min, m/z = 169.2 $[M-H]^-$, 99.65%.

Intermediate 4. *N*-Ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide

First Procedure:

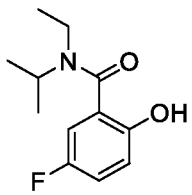


Step 1. N-Ethyl-5-fluoro-N-isopropyl-2-methoxybenzamide



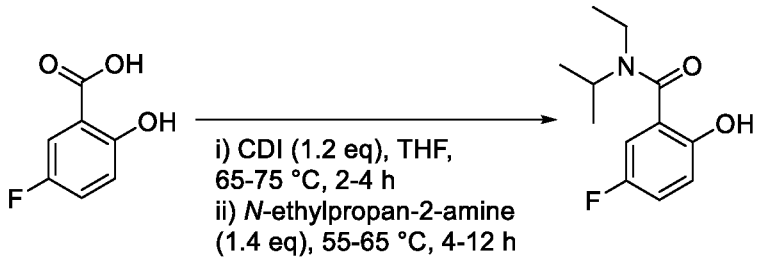
In a dried, 1 L four neck round bottom flask under nitrogen atmosphere, 5-fluoro-2-methoxybenzoic acid (15 g, 88 mmol) was added in DMF (200 mL). To this solution, DIPEA (46.2 mL, 264 mmol), HATU (40.2 g, 106 mmol), and *N*-ethylpropan-2-amine (12.81 mL, 106 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 25% EtOAc in hexane) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide (20.5 g, 78% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (ddd, J = 3.1, 8.0, 9.0 Hz, 1H), 6.99 – 6.90 (m, 1H), 6.85 (dd, J = 4.1, 9.0 Hz, 1H), 3.82 (s, 3H), 3.73 (spt, J = 6.6 Hz, 1H), 3.50 – 3.36 (m, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.19 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H); LCMS (Method D): Rt = 1.78 min, m/z = 240.1 $[M+H]^+$; 79.99%.

Step 2. N-Ethyl-5-fluoro-2-hydroxy-N-isopropylbenzamide



In a dried, 1 L three neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide (20.5 g, 86 mmol) was added in DCM (200 mL). To this solution, BBr_3 (86 mL, 86 mmol, 1M in DCM) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (20% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (200 mL) and extracted with DCM (3 x 200 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (19 g, 97% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 – 9.55 (br s, 1H), 7.02 (dt, *J* = 3.1, 8.7 Hz, 1H), 6.91 (dd, *J* = 3.1, 8.5 Hz, 1H), 6.84 (dd, *J* = 4.5, 8.9 Hz, 1H), 3.74 – 3.58 (m, 1H), 3.40 – 3.19 (m, 2H), 1.26 – 0.97 (m, 9H); LCMS (Method D): Rt = 1.54 min, m/z = 226.2 $[M+H]^+$; 98.33%.

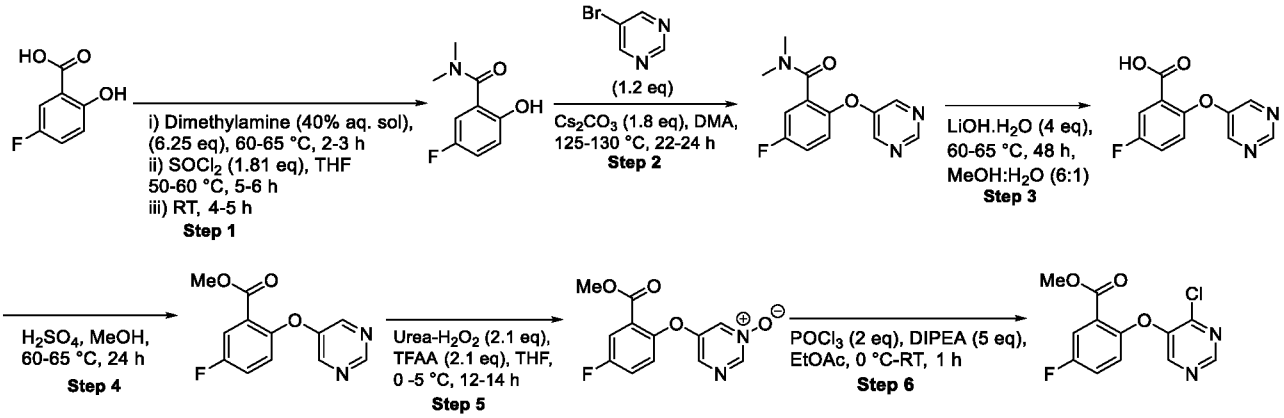
Second Procedure:



Reactor 1 was charged with THF (40.4 kg) and reactor 2 was charged with THF (53.6 kg) under a nitrogen atmosphere. 5-Fluoro-2-hydroxybenzoic acid (17.9 kg, 114.6 moles) was dissolved in reactor 2, and the solution was stirred at 20-30 °C for 1-2 h. CDI (22.6 kg, 139.4 moles) was dissolved in reactor 1, and the reaction was stirred at 65-75 °C for 1-2 h. The reaction mixture in reactor 2 was transferred to reactor 1 dropwise (over 1 h) at 65-75 °C. The reaction was stirred at the same temperature for 1-2 h. The batch was sampled for IPC. The reaction temperature was lowered to 55-65 °C, and *N*-ethylpropan-2-amine (14 kg, 160.6 moles) was added to the dropwise to the reactor 1 over 0.5-2 h. The reaction was stirred at 55-65 °C for 4-10 h. The batch was sampled for IPC. After completion, the reaction was cooled to 0-10 °C, and charged with isopropyl acetate (39.2 kg). To this reaction mixture, aqueous HCl solution (62.6 kg, 20% w/w) was added dropwise over 0.5 h at 0-10 °C, and the solution was stirred at the same temperature for 0.5-2 h. The reaction mixture was allowed to stand at 0-10 °C for 0.5-2 h to separate layers. The organic layer was separated and washed with brine solution (53.7 kg, 10% w/w) at 15-25 °C. The biphasic mixture was allowed to stand for 10-30 min. Both the layers were separated, and the organic layer was concentrated under reduced pressure (bath temperature 45-55 °C) to 3-4 volume. THF (72 kg) was added

to the residue and the mixture was concentrated under reduced pressure (bath temperature 45 °C -55 °C) to 3-4 volume. The same procedure was repeated two times. *n*-Heptane (63 kg) was added to the residue and the mixture was concentrated under reduced pressure (bath temperature 45-55 °C) to 3-4 volume. Once again, *n*-heptane (63 kg) was added to the residue and the mixture was stirred at 0-10 °C for 1-4 h. The suspension was filtered, and the cake was washed with *n*-heptane (25 kg). The wet cake was dried at 40-50 °C to obtain *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (21.8 kg, 84.5% yield). HPLC purity: 99.92%.

Intermediate 5. Methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (Procedure 1)



Step 1. 5-Fluoro-2-hydroxy-N,N-dimethylbenzamide

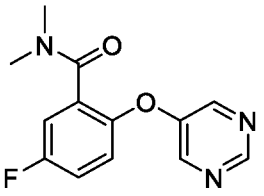


A 40% aqueous dimethylamine solution (140.0 L, 1200.0 mol) was heated at 60-65 °C for 2-3 h to release dimethylamine gas, which was purged into a cooled solution (0-5 °C) of THF (250.0 L).

In another reactor, thionyl chloride (41.0 kg, 347.4 moles) was added to a solution of 5-fluorosalicylic acid (30.0 kg, 192.0 moles) in THF (100.0 L) over a period of 1-2 h. The reaction mixture was heated to 50-60 °C for 5-6 h. After completion of the reaction, as judged by TLC, the reaction mixture was concentrated completely. THF was added and distilled out to remove the remaining thionyl chloride. The acid chloride thus obtained was dissolved in THF (30.0 L) and was added to the dimethylamine-THF solution at 0-5 °C. The reaction mixture was stirred at RT for 4-5 h. After completion of the reaction, the reaction mixture was concentrated under a vacuum below 40 °C. Ice water was added, and the mixture was stirred for 1-2 h at room temperature to precipitate a solid. The solid was filtered and washed with water. The solid was triturated with cyclohexane and centrifuged to give 5-fluoro-2-hydroxy-

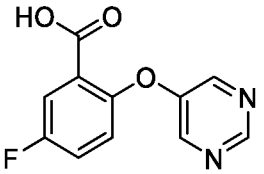
N,*N*-dimethylbenzamide (28.5 kg, 81% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.81 (s, 3H), 2.94 (s, 3H), 6.83-6.87 (m, 1H), 6.92-6.95 (m, 1H), 7.02-7.07 (m, 1H), 9.76 (br, 1H); HPLC (% purity): 99.63%.

Step 2. 5-Fluoro-N,N-dimethyl-2-(pyrimidin-5-yloxy)benzamide



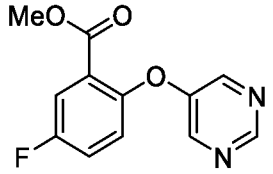
To a solution of 5-fluoro-2-hydroxy-*N*,*N*-dimethylbenzamide (28.0 kg, 153.0 moles) and 5-bromopyrimidine (29.16 kg, 183.0 moles) in dimethyl acetamide (180.0 L) were added cesium carbonate (89.73, 270.0 moles). The reaction mixture was heated to 125-130 °C for 22-24 h. After complete consumption of starting material, as judged by TLC, the reaction mixture was cooled to 35-40 °C and filtered to remove the cesium carbonate. The reaction mixture was concentrated under a vacuum. The residue thus obtained was dissolved in water (84.0 L) and extracted with DCM (2 x 56.0 L). The DCM layer was washed with 10% aqueous sodium hydroxide solution, followed by dilute HCl solution, dried over sodium sulfate, filtered, and concentrated to give 5-fluoro-*N*,*N*-dimethyl-2-(pyrimidin-5-yloxy)benzamide (24.0 kg, 60.1% yield) as a semisolid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.54 (s, 2H), 7.25-7.34 (m, 3H), 2.85 (s, 3H), 2.84 (s, 3H); HPLC (% purity): 86.75%.

Step 3. 5-Fluoro-2-(pyrimidin-5-yloxy)benzoic acid



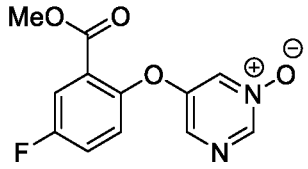
To a solution of 5-fluoro-*N*,*N*-dimethyl-2-(pyrimidin-5-yloxy)benzamide (23.5 kg, 90.03 moles) in 6:1 MeOH/H_2O (140.0 L) was added LiOH.H_2O (15.5 kg, 360.0 moles), and the reaction was heated at 60-65 °C for 48 h. The reaction mixture was cooled to 40 °C, and the methanol was distilled out in vacuum below 40 °C. The residue thus obtained was dissolved in water. The aqueous layer was washed with ethyl acetate. The aqueous layer was treated with activated carbon and filtered on Hyflo. The aqueous layer was acidified with concentrated HCl (1.5 L) to pH ~1.0-2.0 to precipitate a solid. This solid was filtered, washed with water, and dried at 40-45 °C to give 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (13.5 kg, 64.1% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (br s, 1H), 8.92 (s, 1H), 8.46 (s, 2H), 7.69-7.71 (m, 1H), 7.52- 7.57 (m, 1H), 7.38- 7.42 (m, 1H); HPLC (% purity): 96.94%.

Step 4. Methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate



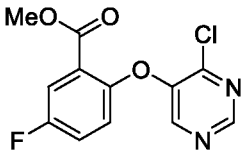
To a cooled solution of 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (13.5 kg, 57.69 moles) in methanol (90.0 L) was added sulfuric acid (2.16 L), and the reaction was heated at 60-65 °C for 24 h. The reaction mixture was cooled to room temperature, and the methanol was distilled out completely under reduced pressure. The residue thus obtained was dissolved in DCM (54.0 L). The DCM layer was washed with 5% sodium bicarbonate solution and saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (9.6 kg, 67.1% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.50 (s, 2H), 7.72-7.75 (m, 1H), 7.57- 7.62 (m, 1H), 7.41- 7.45 (m, 1H), 3.73 (s, 3H); HPLC (% purity): 98.37%; assay by Q-NMR (%): 99.21%.

Step 5. 5-(4-Fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine 1-oxide



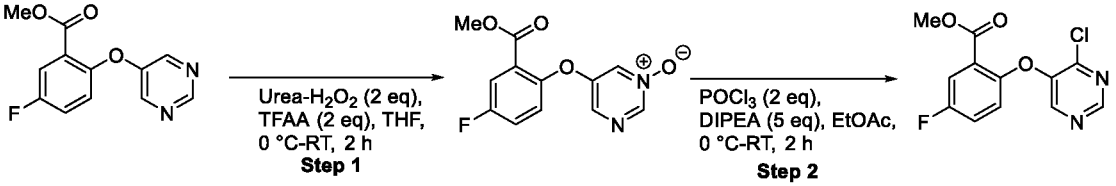
To a cooled solution of methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (9.6 kg, 38.7 moles) in THF (150 L) was added UHP (7.64 kg, 81.2 moles) at 0-5 °C (over a period of 30 min), and the reaction was stirred for 10 min at 0-5 °C. TFAA (17.0 kg, 81.0 moles) was then added dropwise over 30-40 min at 0-5 °C. The reaction was stirred at 0-5 °C for 12-14 h. After complete consumption of starting material, as judged by TLC, the reaction mixture was quenched by the addition of 5% $NaHCO_3$ solution at 0-5 °C. DCM (60.0 L) was then added at 5-10 °C, and the mixture was stirred for 20 min. The aqueous and organic layers were separated. The organic layer was washed with 5% $NaHCO_3$. Aqueous sodium thiosulfate solution was then added to the organic layer (DCM layer), and the mixture was stirred for 12 hours at 10 °C. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine-1-oxide (5.12 kg, 50.0% yield) as solid. ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.86 (s, 1H), 8.44 (s,1H), 8.01 (s, 1H), 7.72-7.75 (m, 1H), 7.59- 7.64 (m, 1H), 7.49 - 7.52 (m, 1H), 3.76 (s, 3H); HPLC (% purity): 99.60%.

Step 6. Methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate

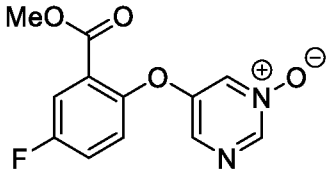


In a 100 mL two neck round bottom flask under a nitrogen atmosphere, 5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine 1-oxide (20 g, 76 mmol) was added in EtOAc (200 mL). To this solution, DIPEA (65.3 mL, 378 mmol) was added at 0 °C, and the reaction was stirred at the same temperature for 15 min. To this reaction mixture, $POCl_3$ (14.15 mL, 151 mmol) was added dropwise at 0 °C. The reaction was warmed to RT and stirred for 1 h. The reaction was monitored by TLC (50% EtOAc in hexane). The reaction was concentrated under reduced pressure to afford crude compound. The crude compound was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 25% EtOAc in hexane) to obtain methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (16.5 g, 72.2% yield) as a solid. ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.30 (s, 1H), 7.76 (dd, J = 3.1, 8.8 Hz, 1H), 7.61 (ddd, J = 3.3, 7.9, 9.0 Hz, 1H), 7.46 (dd, J = 4.6, 9.0 Hz, 1H), 3.75 (s, 3H); LCMS (Method G): Rt = 1.74 min, m/z = 283.1 $[M+H]^+$; 93.65%.

Intermediate 5. Methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (Procedure 2)



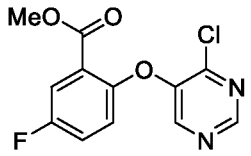
Step 1. 5-(4-Fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine 1-oxide



To a stirred solution of methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (5 g, 20.14 mmol) in THF (10 mL), urea hydrogen peroxide (3.79 g, 40.3 mmol) was added, and followed by TFAA (8.46 g, 40.3 mmol) was added dropwise at 0 °C. The reaction was allowed to stir at RT for 2 h. The reaction was monitored by TLC (5% MeOH in DCM). The reaction was diluted with saturated aqueous sodium bicarbonate solution (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with saturated sodium thiosulfate (100 mL) and brine solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 5-(4-fluoro-2

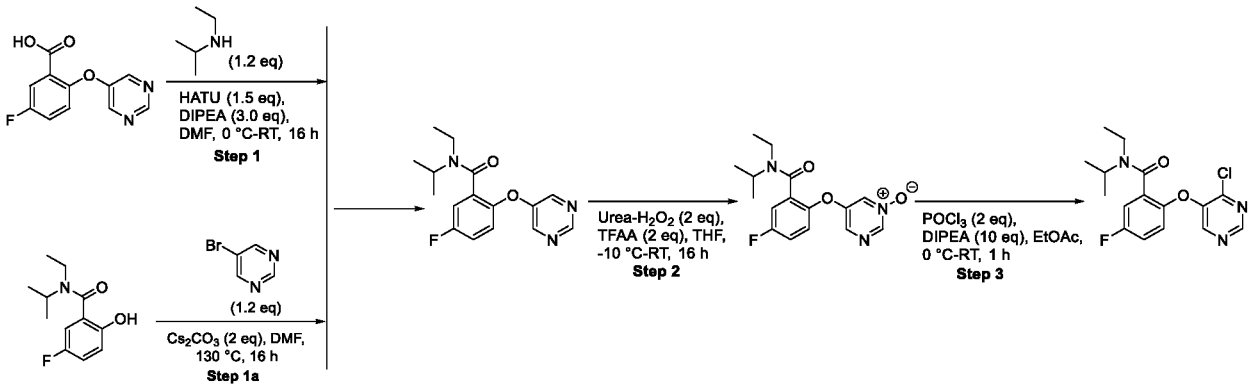
(methoxycarbonyl)phenoxy)pyrimidine 1-oxide (5.32 g, 93% yield) as a sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (d, J = 1.5 Hz, 1H), 8.44 (dd, J = 1.7, 2.3 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.74 (dd, J = 3.3, 8.8 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.51 (dd, J = 4.6, 9.1 Hz, 1H), 3.77 (s, 3H); LCMS (Method D): Rt = 1.30 min, m/z = 265.2 $[M+H]^+$; 94.67%. This material was used without further purification.

Step 2. Methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate

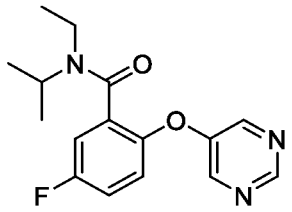


In a dried, 500 mL three neck round bottom flask under nitrogen atmosphere, 5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine 1-oxide (5.9 g, 22.33 mmol) was added in EtOAc (50 mL). To this reaction mixture, DIPEA (19.45 mL, 112 mmol) and $POCl_3$ (4.18 mL, 44.7 mmol) were added at 0 °C. The reaction was stirred at RT for 2 h. The reaction was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 30% EtOAc in hexane) to obtain methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (2.5 g, 39.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.30 (s, 1H), 7.77 (dd, J = 3.2, 8.8 Hz, 1H), 7.61 (ddd, J = 3.2, 7.8, 9.1 Hz, 1H), 7.46 (dd, J = 4.6, 9.0, 1H), 3.75 (s, 3H); LCMS (Method B): Rt = 2.41 min, m/z = 283.0 $[M+H]^+$; 93.55%.

Intermediate 6. 2-((4-Chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Procedure 1)

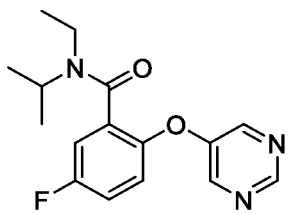


Step 1. N-Ethyl-5-fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)benzamide



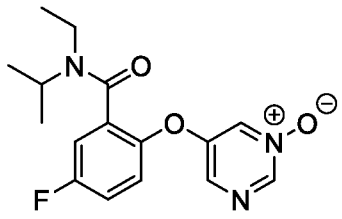
In a dried, 500 mL two neck round bottom flask under nitrogen atmosphere, 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (29.485 g, 126 mmol) was added in DMF (300 mL). To this solution, DIPEA (66.0 mL, 378 mmol), and HATU (71.8 g, 189 mmol) were added at 0 °C, followed by *N*-ethylpropan-2-amine (18.29 mL, 151 mmol) at RT. The reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (500 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with cold water (500 mL) and brine solution (3 x 200 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 87% EtOAc in hexane) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (41.2 g, 84% yield) as a sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.56 - 8.45 (m, 2H), 7.40 - 7.30 (m, 3H), 3.74 (spt, J = 6.7 Hz, 1H), 3.45 - 3.33 (m, 1H), 3.23 - 3.10 (m, 1H), 1.16 – 1.02 (6 H), 1.03 – 0.96 (m, 3H); LCMS (Method B): Rt = 2.26 min, m/z = 304.3 $[M+H]^+$; 77.68%.

Step 1a. N-Ethyl-5-fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)benzamide



In a dried, 1 L three neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (19 g, 84 mmol) was added in DMF (200 mL). To this reaction mixture, Cs_2CO_3 (55.0 g, 169 mmol) and 5-bromopyrimidine (16.09 g, 101 mmol) were added at RT. The reaction was stirred at 130 °C for 16 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (200 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 70% EtOAc in hexane) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (17.1 g, 56.1% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.53 – 8.50 (m, 2H), 7.38 – 7.32 (m, 3H), 3.73 (spt, J = 6.6 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.21 – 3.11 (m, 1H), 1.26 – 1.02 (m, 6H), 1.02 – 0.85 (m, 3H); LCMS (Method D): Rt = 1.58 min, m/z = 304.1 $[M+H]^+$; 83.91%.

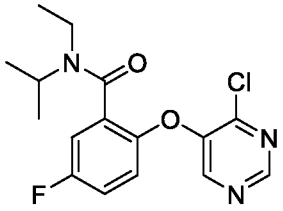
Step 2. 5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide



Step 2 was performed following the same procedure in two batches, 2 x 20.7 g batches.

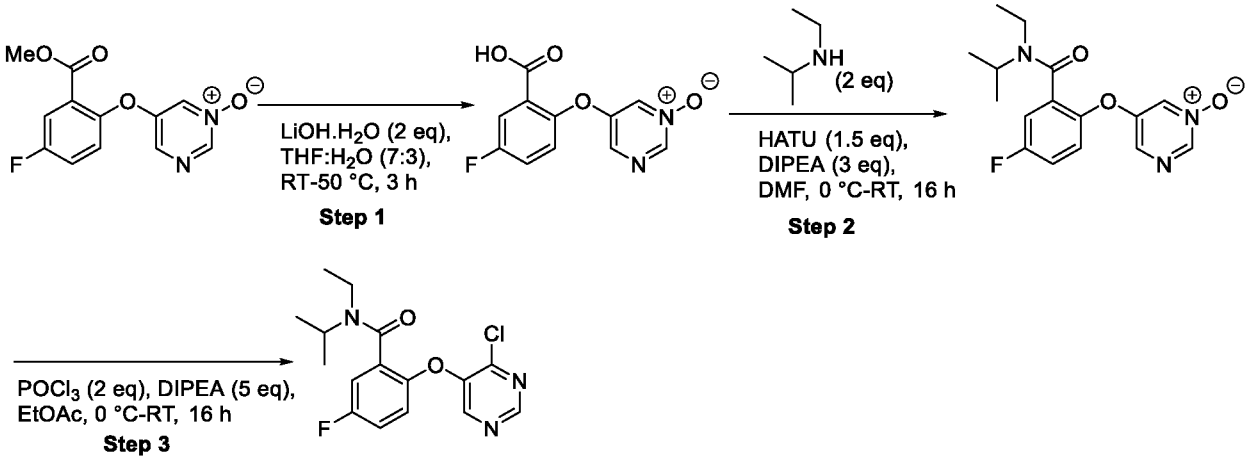
In a dried, 500 mL three neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (20.7 g, 68.2 mmol) was added in THF (200 mL). To this solution, urea hydrogen peroxide (12.84 g, 136 mmol) and TFAA (19.28 mL, 136 mmol)) were added slowly at -10 °C. The reaction was stirred at RT for 16 h. The reaction was monitored by TLC (100% EtOAc). The reaction mixture from both batches (2 x 20.7 g) was combined, cooled to 0 °C, quenched with aqueous sodium bicarbonate solution (200 mL), and extracted with EtOAc (2 x 250 mL). The combined organic layer was washed with aqueous sodium thiosulfate solution (500 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford 5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (46.15 g, 86.02% combined yield) as a gummy liquid. LCMS (Method B): Rt = 1.87 min, m/z = 320.0 $[M+H]^+$; 57.84%.

Step 3. 2-((4-Chloropyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

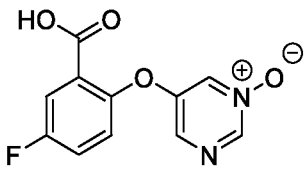


In a dried, 500 mL two neck round bottom flask under nitrogen atmosphere, 5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (10 g, 31.3 mmol) was added in EtOAc (100 mL). To this solution, DIPEA (54.7 mL, 313 mmol) and phosphoryl trichloride (5.86 mL, 62.6 mmol) were added at 0 °C under a nitrogen atmosphere. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 58% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (3.049 g, 27.3% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 – 8.76 (m, 1H), 8.34 – 8.27 (m, 1H), 7.43 –7.33 (m, 3H), 3.72 (spt, J = 6.6 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.24 – 3.12 (m, 1H), 1.18 – 1.07 (m, 6H), 1.05 – 0.98 (m, 3H); LCMS (Method B): Rt = 2.36 min, m/z = 338.0 $[M+H]^+$; 94.54%.

Intermediate 6. 2-((4-Chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Procedure 2)

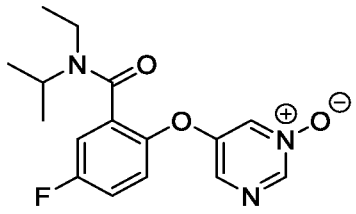


Step 1. 5-(2-Carboxy-4-fluorophenoxy)pyrimidine 1-oxide



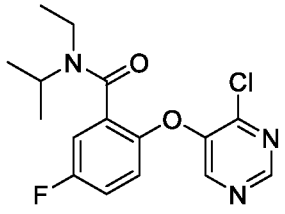
To a stirred solution of 5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine 1-oxide (10 g, 37.8 mmol) in THF (70 mL) and water (30 mL), LiOH (1.813 g, 76 mmol) was added at RT. The reaction was stirred at 50 °C for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure and dissolved in water (20 mL). The aqueous layer was acidified with 1.5 N HCl (pH ~6). The solid was filtered and co-distilled with toluene to obtain 5-(2-carboxy-4-fluorophenoxy)pyrimidine 1-oxide (9.1 g, 61.4% yield) as a solid. LCMS (Method G): Rt = 0.57 min, m/z = 251.2 $[M+H]^+$; 63.88%.

Step 2. 5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide



In a dried, 500 mL round bottom flask under nitrogen atmosphere, 5-(2-carboxy-4-fluorophenoxy)pyrimidine 1-oxide (8.0 g, 32.0 mmol) was added in DMF (50 mL). To this solution, DIPEA (17.08 mL, 96 mmol), HATU (18.24 g, 48.0 mmol), and *N*-ethylpropan-2-amine (7.74 mL, 64.0 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was quenched with ice-cold water (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with ice-cold water (100 mL) and brine solution (2 x 100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude product as a sticky liquid. The crude product was purified by silica gel flash column chromatography, eluted at 100% EtOAc to obtain 5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (7.9 g, 53.4% yield) as a sticky liquid. LCMS (Method I): Rt = 1.95 min, m/z = 320.1 $[M+H]^+$; 69.73%.

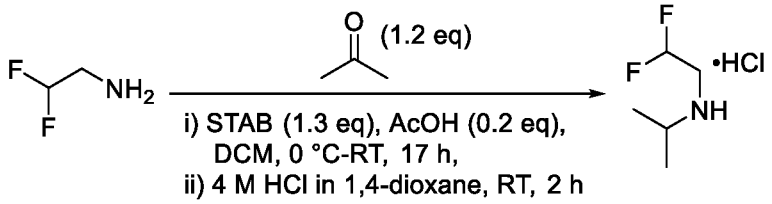
Step 3. 2-((4-Chloropyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



In a 500 mL two neck round bottom flask under nitrogen atmosphere, 5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (5.7 g, 17.85 mmol) was added in EtOAc (60 mL). DIPEA (15.89 mL, 89 mmol) was added at 0 °C to this solution, and

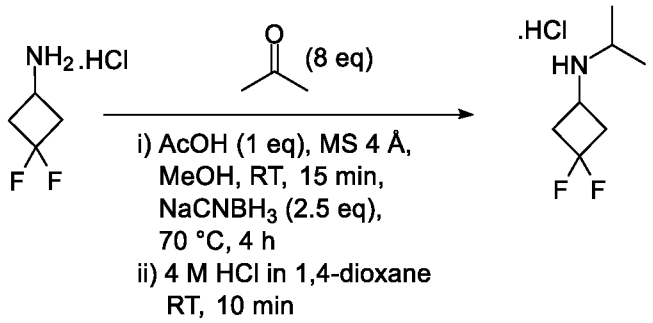
the reaction was stirred for 5 min, followed by $POCl_3$ (3.34 mL, 35.7 mmol) added dropwise at 0 °C. The reaction was warmed to RT and stirred for 16 h. The reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 50% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (2.6 g, 41.8% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 – 8.77 (m, 1H), 8.36 – 8.25 (m, 1H), 7.42 – 7.33 (m, 3H), 3.72 (spt, J = 6.4 Hz, 1H), 3.41 – 3.35 (m, 1H), 3.23 – 3.11 (m, 1H), 1.18 – 1.08 (m, 6H), 1.04 – 0.98 (m, 3H); LCMS (Method B): Rt = 2.04 min, m/z = 337.8 $[M+H]^+$; 97.52%.

Intermediate 7. *N*-(2,2-Difluoroethyl)propan-2-amine hydrochloride



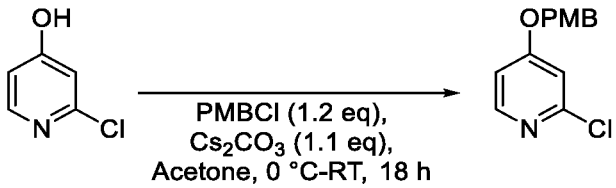
In a 2 L four neck round bottom flask under nitrogen atmosphere, 2,2-difluoroethan-1-amine (21.74 mL, 308 mmol) was added in DCE (500 mL), and the solution was cooled to 0 °C. To this solution, acetone (27.6 mL, 370 mmol) and acetic acid (3.53 mL, 61.7 mmol) were added, and the reaction was stirred at RT for 1 h. The reaction was again cooled to 0 °C, and sodium triacetoxyborohydride (85 g, 401 mmol) was added portion-wise over 15 min. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (60% EtOAc in hexane). After completion, the reaction was diluted with DCM (500 mL) and washed with 10% $NaHCO_3$ solution (3 x 500 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was transferred to 2 L single neck round bottom flask and cooled to 0 °C. To this solution, 4 M HCl in 1,4 dioxane (300 mL) was added, and the mixture was stirred for 2 h at RT. The reaction was concentrated under reduced pressure to obtain *N*-(2,2-difluoroethyl)propan-2-amine hydrochloride (33 g, 67% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 – 9.65 (br s, 2H), 6.69 – 6.38 (m, 1H), 3.53 – 3.35 (m, 3H), 1.28 (d, J = 6.5 Hz, 6H).

Intermediate 8. 3,3-Difluoro-*N*-isopropylcyclobutan-1-amine hydrochloride



To a stirred solution of 3,3-difluorocyclobutan-1-amine hydrochloride (5 g, 34.8 mmol) in dry MeOH (20 mL), acetone (20.64 mL, 279 mmol), 4 Å molecular sieves (5 g), and acetic acid (1.992 mL, 34.8 mmol) were added at RT under nitrogen atmosphere. The reaction was stirred at RT for 15 min, then $NaCNBH_3$ (5.47 g, 87 mmol) was added, and the reaction was stirred at 70 °C for 4 h. The reaction was concentrated under reduced pressure to afford crude material. To this crude, EtOAc (100 mL) was added, and the mixture was filtered through a Celite® pad, and the pad was washed with EtOAc (50 mL). The filtrate was washed with sodium bicarbonate solution (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was transferred to a round bottom flask, and 4 M HCl in dioxane (10 mL) was added. The reaction was stirred at RT for 10 min, then was concentrated under reduced pressure to afford crude 3,3-difluoro-*N*-isopropylcyclobutan-1-amine hydrochloride (5.6 g, 87% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.78 (br s, 2H), 3.82 – 3.65 (m, 1H), 3.29 – 3.19 (m, 1H), 3.15 – 2.84 (m, 4H), 1.24 (d, J = 6.6 Hz, 6H). This material was used without further purification.

Intermediate 9. 2-Chloro-4-((4-methoxybenzyl)oxy)pyridine

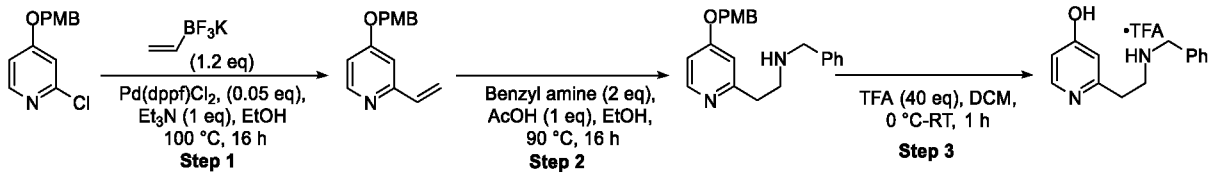


The reaction was performed following the same procedure in two batches (2 x 150 g).

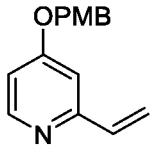
In a 10 L four neck round bottom flask under nitrogen atmosphere, 2-chloropyridin-4-ol (150 g, 1158 mmol) was added in acetone (2.5 L) at RT, and the reaction was cooled to 0 °C. To this cooled solution, Cs_2CO_3 (415 g, 1274 mmol) was added, then 4-methoxybenzyl chloride (0.189 L, 1390 mmol) was added slowly using a dropping funnel. The reaction was stirred at RT for 18 h. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, crude material from these two batches was combined, filtered, and

washed with acetone (2 x 1 L). The filtrate was concentrated under reduced pressure, and the residue was diluted with water (1 L) and extracted with EtOAc (3 x 2.5 L). The combined organic layer was washed with brine solution (2 x 1 L), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted in 20% EtOAc in hexane) to obtain 2-chloro-4-((4-methoxybenzyl)oxy)pyridine (275 g, 44.3% yield, combined yield for 300 g batch) as a solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.21 (d, *J* = 5.79 Hz, 1 H), 7.40 (d, *J* = 8.55 Hz, 2 H), 7.18 (d, *J* = 2.10 Hz, 1 H), 7.06 (dd, *J* = 5.79, 2.24 Hz, 1 H), 6.97 (d, *J* = 8.68 Hz, 2 H), 5.15 (s, 2 H), 3.76 (s, 3 H); LCMS (Method G): Rt = 1.96 min, m/z = 250.0 $[M+H]^+$, 93.16%.

Intermediate 10. 2-(2-(Benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid

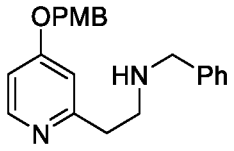


Step 1. 4-((4-Methoxybenzyl)oxy)-2-vinylpyridine



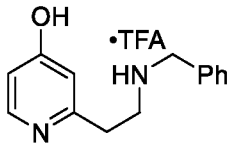
In a 10 L three neck round bottom flask, ethanol (3.5 L) was added, and the solution was degassed by purging with argon gas for 15 min. To this solution, 2-chloro-4-((4-methoxybenzyl)oxy)pyridine (170 g, 681 mmol), potassium trifluoro(vinyl)borate (109 g, 817 mmol), TEA (96 mL, 681 mmol), and $PdCl_2$(dppf) (24.91 g, 34.0 mmol) were added at RT. The reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with EtOAc (2 x 500 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by flash column chromatography using EtOAc and hexane (product was eluted at 20% EtOAc in hexane) to obtain 4-((4-methoxybenzyl)oxy)-2-vinylpyridine (110 g, 63.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.35 (d, *J* = 5.66 Hz, 1H), 7.41 (d, *J* = 8.55 Hz, 2H), 7.14 (d, *J* = 2.37 Hz, 1H), 6.96 (d, *J* = 8.68 Hz, 2H), 6.92 (dd, *J* = 2.50, 5.66 Hz, 1H), 6.75 (dd, *J* = 10.72, 17.43 Hz, 1H), 6.24 (dd, *J* = 1.64, 17.43 Hz, 1H), 5.45 (dd, *J* = 1.64, 10.72 Hz, 1H), 5.13 (s, 2 H), 3.77 (s, 3 H); LCMS (Method G): Rt = 1.97 min, m/z = 242.2 $[M+H]^+$, 94.67%.

Step 2. N-Benzyl-2-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)ethan-1-amine



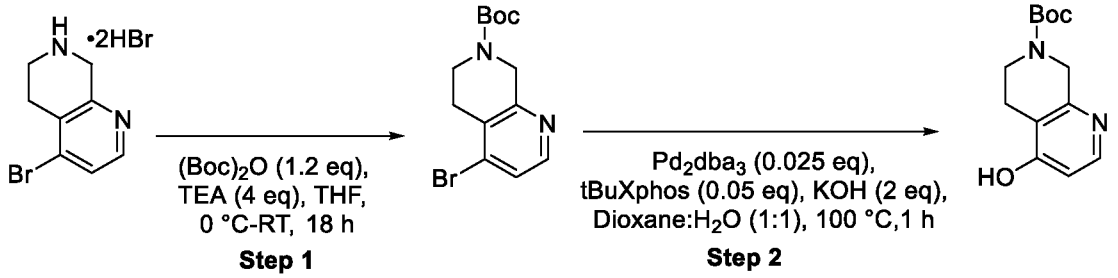
To a stirred solution of 4-((4-methoxybenzyl)oxy)-2-vinylpyridine (100 g, 414 mmol) in ethanol (2 L), benzylamine (91 mL, 829 mmol) and acetic acid (23.73 mL, 414 mmol) were added under nitrogen atmosphere. The reaction was stirred at 90 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to RT and concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to afford *N*-benzyl-2-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)ethan-1-amine (102 g, 56.1% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 5.75 Hz, 1H), 7.38 (d, J = 8.76 Hz, 2H), 7.34 - 7.33 (m, 2H), 7.31 - 7.29 (m, 5H), 6.96 - 6.94 (m, 2H), 5.07 (s, 2H), 3.76 (s, 3H), 3.75 (s, 2H), 2.83 - 2.81 (m, 4H), -NH proton not observed; LCMS (Method D): Rt = 1.96 min, m/z = 349.0 $[M+H]^+$, 79.48%.

Step 3. 2-(2-(Benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid

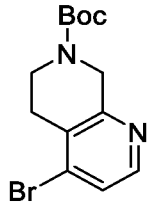


To a stirred solution of *N*-benzyl-2-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)ethan-1-amine (50 g, 143 mmol) in DCM (320 mL), TFA (439 mL, 5740 mmol) was added over 20 min at 0 °C. The reaction was slowly warmed to RT and stirred for 1 h. The reaction turned purple from its initial pale-yellow color. The progress of the reaction was monitored by TLC (15% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 15% MeOH in DCM) to obtain 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (48.5 g, 75% yield) as a semi-solid. LCMS (Method G): Rt = 1.15 min, m/z = 229.1 $[M+H]^+$, 76.16%.

Intermediate 11. ***tert*-Butyl 4-hydroxy-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate**

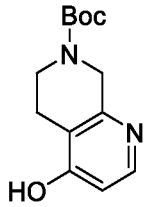


Step 1. tert-Butyl 4-bromo-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



To a solution of 4-bromo-5,6,7,8-tetrahydro-1,7-naphthyridine dihydrobromide (5.0 g, 13.34 mmol) in THF (50 mL), TEA (7.50 mL, 53.3 mmol), and $(Boc)_2O$ (3.68 mL, 16.00 mmol) were added at 0 °C. The reaction was stirred at RT for 18 h. The reaction was monitored by TLC (30% EtOAc in hexane). The reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 45% EtOAc in hexane) to obtain *tert*-butyl 4-bromo-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (4.1 g, 96% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, J = 5.3 Hz, 1H), 7.60 (d, J = 5.3 Hz, 1H), 4.55 (s, 2H), 3.65 (t, J = 5.9 Hz, 2H), 2.77 (t, J = 5.9 Hz, 2H), 1.43 (s, 9H); LCMS (Method G): Rt = 1.96 min, m/z = 313.2 $[M+H]^+$; 98.29%.

Step 2. tert-Butyl 4-hydroxy-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



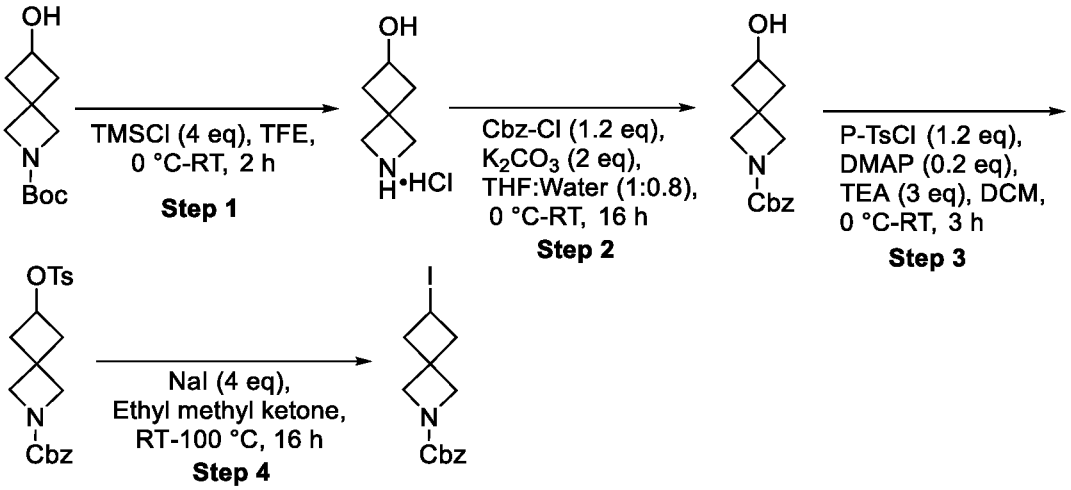
A solution of *tert*-butyl 4-bromo-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (4.1 g, 13.09 mmol) and KOH (1.469 g, 26.2 mmol) in 1,4-dioxane (15 mL) and water (15 mL) was purged with nitrogen for 5 min. To this mixture, *t*BuXPhos (0.278 g, 0.655 mmol) and $Pd_2(dba)_3$ (0.300 g, 0.327 mmol) were added at RT under a nitrogen atmosphere. The reaction was stirred at 100 °C for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). After

completion, the reaction was concentrated under reduced pressure to remove dioxane. The crude was diluted with water (40 mL) and extracted with 50% EtOAc in hexane (2 x 50 mL) to remove impurities. The aqueous layer was neutralized with saturated ammonium chloride solution and extracted with 20% MeOH in DCM (10 x 50 mL). (**Note**: The product was water soluble). Therefore, the mixture was extracted multiple times to make sure the compound was removed from the aqueous layer). The combined organic extract was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-hydroxy-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (3.2 g, 96% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (br s, 1H), 7.56 (br s, 1H), 5.97 (d, J = 7.1 Hz, 1H), 4.32 (br s, 2H), 3.53 – 3.48 (br s, 2H), 2.37 – 2.32 (br s, 2H), 1.43 (s, 9H); LCMS (Method D): Rt = 1.27 min, m/z = 251.1 $[M+H]^+$; 98.27%. In some cases, the crude product was used without neutralizing with NH_4Cl solution.

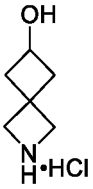
Intermediate 12. 2-Azaspiro[3.3]heptan-6-ol hydrochloride

Intermediate 13. Benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate

Intermediate 14. Benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate

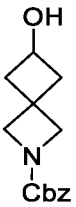


Step 1. 2-Azaspiro[3.3]heptan-6-ol hydrochloride (**Intermediate 12**)



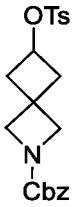
In a 3 L three neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (200 g, 938 mmol) was added in 2,2,2-trifluoroethanol (2.5 L). The reaction was cooled to 0 °C, and TMSCl (0.476 L, 3751 mmol) was added slowly through a dropping funnel. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was triturated with ethyl acetate (2 x 500 mL) and dried under reduced pressure to obtain 2-azaspiro[3.3]heptan-6-ol hydrochloride (130 g, 92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (br s, 2H), 5.11 (d, J = 6.00 Hz, 1H), 3.99 – 3.90 (m, 1H), 3.88 (s, 2H), 3.84 (s, 2H), 2.49 – 2.43 (m, 2H), 2.01 – 1.91 (m, 2H); LCMS (Method G): Rt = 0.41 min, m/z = 114.1 $[M+H]^+$, 99.40%. This material was used without further purification.

Step 2. Benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (**Intermediate 13**)



In a 3 L three neck round bottom flask under a nitrogen atmosphere, 2-azaspiro[3.3]heptan-6-ol hydrochloride (130 g, 869 mmol) was added in THF (1 L) and water (800 mL) at RT. The reaction was cooled to 0 °C, and K_2CO_3 (240 g, 1738 mmol) was added. To this reaction mixture, benzyl chloroformate (0.147 L, 1043 mmol) was added slowly using a dropping funnel. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was diluted with water (1.5 L) and extracted with EtOAc (2 x 2.5 L). The combined organic layer was washed with brine solution (1 L), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 80% EtOAc in hexane) to obtain benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (210 g, 93% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 - 7.28 (m, 5H), 5.03 - 4.99 (m, 3H), 3.98 - 3.79 (m, 5H), 2.45 - 2.36 (m, 2H), 1.98 - 1.89 (m, 2H); LCMS (Method G): Rt = 1.47 min, m/z = 248.2 $[M+H]^+$, 95.12%.

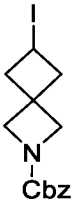
Step-3. Benzyl 6-(tosyloxy)-2-azaspiro[3.3]heptane-2-carboxylate



In a 5 L three neck round bottom flask under a nitrogen atmosphere, benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (210 g, 849 mmol) was added in DCM (2 L). The reaction was cooled to 0 °C, and TEA (0.355 L, 2548 mmol) and DMAP (20.75 g, 170 mmol) were added. To this reaction mixture, *p*-toluenesulfonyl chloride (194 g, 1019 mmol) was added portion-wise at the same temperature. The resulting reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was diluted with water (1 L) and extracted with DCM (2 x 2 L). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane followed by DCM (product was eluted at 100% DCM) to obtain benzyl 6-(tosyloxy)-2-azaspiro[3.3]heptane-2-carboxylate (270 g, 79% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J = 8.00 Hz, 2H), 7.48 (d, J = 8.00 Hz, 2H), 7.39 - 7.28 (m, 5H), 4.99 (s, 2H), 4.79 - 4.67 (m, 1H), 3.97 - 3.78 (m, 4H),

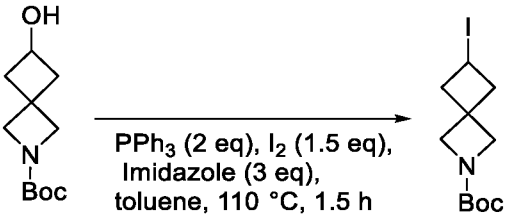
2.48 - 2.44 (m, 2H), 2.43 (s, 3H), 2.27 - 2.20 (m, 2H); LCMS (Method B): Rt = 2.66 min, m/z = 402.2 $[M+H]^+$, 99.59%.

Step-4. Benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (**Intermediate 14**)



In a 3 L three neck round_-bottom flask under a nitrogen atmosphere, benzyl 6-(tosyloxy)-2-azaspiro[3.3]heptane-2-carboxylate (270 g, 673 mmol) was added in ethyl methyl ketone (2 L). To this solution, sodium iodide (403 g, 2690 mmol) was added portion-wise at RT, and the reaction was heated to 100 °C for 16 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was cooled to RT, diluted with water (2 L), and extracted with EtOAc (3 x 1.5 L). The combined organic layer was washed with brine solution (1 L), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (205 g, 81% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 - 7.29 (m, 5H), 5.01 (s,2 H), 4.43 (p, J = 8Hz, 1H), 4.03 - 3.89 (m, 4H), 2.96 - 2.87 (m, 2H), 2.72 - 2.62 (m, 2H); LCMS (Method D): Rt = 2.54 min, m/z = 358.1 $[M+H]^+$, 94.78%.

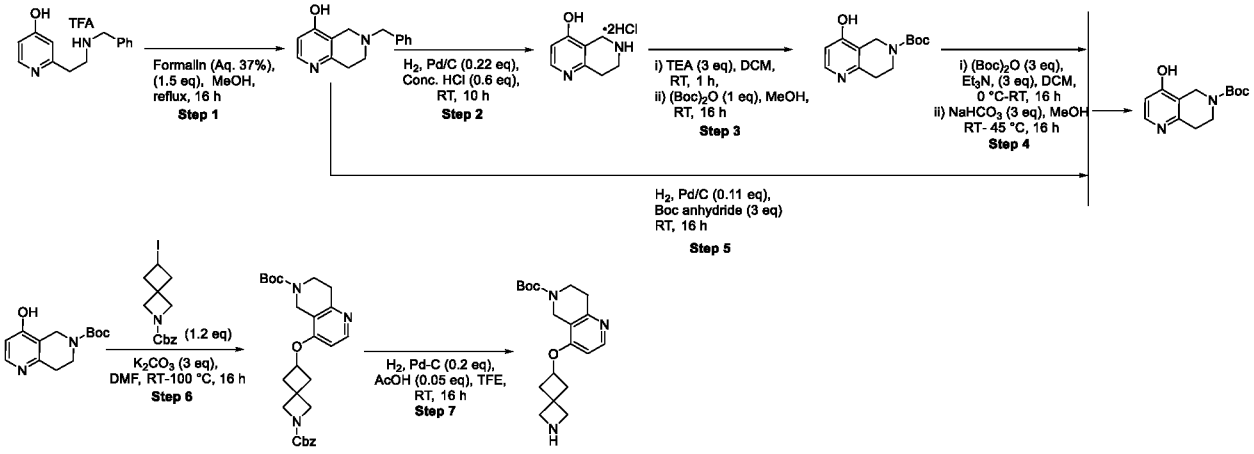
Intermediate 15. *tert*-Butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate



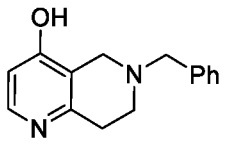
To a solution of *tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (*tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (25 g, 117 mmol) in toluene (250 mL), imidazole (23.94 g, 352 mmol), triphenylphosphine (61.5 g, 234 mmol) and iodine (44.6 g, 176 mmol)) were added at RT. The reaction was stirred at 110 °C for 1.5 h. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was cooled to RT, and the solvent was evaporated under reduced pressure. To this residue, water (500 mL) was added, and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous sodium sulfate,

and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 20-25% EtOAc in hexane) to obtain *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (25 g, 63.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.43 (p, J = 7.8 Hz, 1H), 3.85 (br s, 4H), 2.95 – 2.83 (m, 2H), 2.70 – 2.60 (m, 2H), 1.36 (s, 9H); LCMS (Method G): Rt = 2.11 min, m/z: 268.1 $[M-56]^+$, 96.11%.

Intermediate 16. *tert*-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



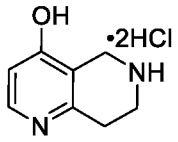
Step 1. 6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (90 g, 263 mmol) in MeOH (2.5 L), formaldehyde solution (29.4 mL, 394 mmol; 37 wt% in water) was added slowly at RT. The reaction was stirred at 70 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 15% MeOH in DCM) to obtain 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (63 g, 99% yield) as semisolid ^{1}H NMR (400 MHz, methanol-d_4) δ 11.91 (brs, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.56 - 7.42 (m, 5H), 6.17 (d, J = 6.8 Hz, 1H), 4.33 (br s, 2H), 3.78 (br s, 2H), 3.33 (br s, 2H), 2.99 - 2.90 (m, 2H); LCMS (Method G): Rt = 1.26 min, m/z = 241.1 $[M+H]^+$, 98.99%.

Note: Traces of TFA remained with the product.

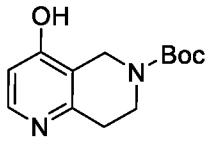
Step 2. 5,6,7,8-Tetrahydro-1,6-naphthyridin-4-ol dihydrochloride ***(Procedure 1)***



Step 2 was performed in three batches (16 g and 2 x 21 g).

In a 100 mL round bottom flask under an argon atmosphere, 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (16 g, 66.6 mmol) was dissolved in MeOH (200 mL). To this solution, concentrated HCl (3.33 mL, 39.9 mmol) and Pd-C (16 g, 15.03 mmol) were added at RT. The reaction was stirred at RT for 10 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction mixtures from all three batches were combined and filtered through a Celite® pad, and the pad was washed with MeOH (2 x 2 L). The filtrate was concentrated under reduced pressure to obtain 5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol dihydrochloride (37 g, 68.7% combined yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.53 (br s, 2H), 7.98 (d, J = 7.0 Hz, 1H), 6.54 (d, J = 6.9 Hz, 1H), 3.95 (s, 2H), 3.39 (br t, J = 5.9 Hz, 2H), 3.00 (br t, J = 5.9 Hz, 2H), -OH proton was not observed; LCMS (Method G): Rt = 0.31, m/z = 151.1 $[M+H]^+$, 94.28%.

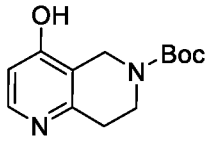
Step 3. tert-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of 5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol dihydrochloride (14.6 g, 65.4 mmol) in DCM (150 mL), TEA (27.4 mL, 196 mmol) was added at RT and stirred for 1 h. The reaction was concentrated under reduced pressure, the residue was dissolved in MeOH (150 mL), and $(Boc)_2O$ (15.03 mL, 65.4 mmol) was added. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (20 g) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (br s, 1H), 7.62 (d, J = 7.2 Hz, 1H), 6.08 (d, J = 7.2 Hz, 1H), 4.11 (s, 2H), 3.56 (t, J = 5.8 Hz, 2H), 2.63 (t, J = 5.8 Hz, 2H), 1.43 (s, 9H); (Method G): Rt = 1.26 min, m/z = 251.1 $[M+H]^+$, 99.58%. Di-boc product was also observed.

Note: ^{1}H NMR showed the peaks for triethylamine hydrochloride along with the product. To remove this Et_3N.HCl salt, step 4 (diboc followed by mono deboc) was performed.

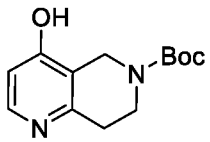
Step 4. tert-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a solution of *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (20 g, 80 mmol) in DCM (200 mL), TEA (33.38 mL, 240 mmol) was added at 0 °C. To this reaction mixture, $(Boc)_2O$ (55.07 mL, 240 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with ice-cold water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((*tert*-butoxycarbonyl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (26 g, 80% yield) as a semi-solid. LCMS (Method G): Rt = 1.83, m/z = 351.3 $[M+H]^+$, 90.92%. This material was used without further purification.

In a 1 L two neck round bottom flask under nitrogen atmosphere, the crude *tert*-butyl 4-((*tert*-butoxycarbonyl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (26 g, 74.2 mmol) was dissolved in methanol (250 mL). To this solution, sodium bicarbonate (18.70 g, 223 mmol) was added, and the reaction was stirred at 45 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with methanol (2 x 250 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (15 g, 80% yield) as a solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 7.56 (br s, 1H), 6.00 (d, J = 7.3 Hz, 1H), 4.09 (s, 2H), 3.55 (t, J = 5.8 Hz, 2H), 2.61 (t, J = 5.8 Hz, 2H), 1.43 (s, 9H); LCMS (Method B): Rt = 1.56 min, m/z = 251.0 $[M+H]^+$, 98.64%.

Step 5. tert-Butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate ***(Procedure 2)***



In a 2 L three neck round bottom flask under an argon atmosphere, 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (35 g, 146 mmol) was added in MeOH (350 mL). To this solution, Pd-C (17.5 g, 16.44 mmol) and $(Boc)_2O$ (101 mL, 437 mmol) were added, and the

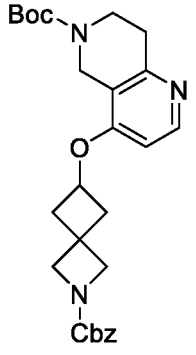
reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (28 g, 74.8% yield) as fluffy solid. 1H NMR (400 MHz, DMSO-d_6): δ 7.99 (br s, 1 H), 6.57 (br s, 1 H), 4.25 (s, 2 H), 3.61 (br t, J = 5.32 Hz, 2 H), 2.79 (br t, J = 4.94 Hz, 2 H), 1.43 (m, 9 H), -OH proton not observed; LCMS (Method D): Rt = 1.16 min, m/z = 251.2 $[M+H]^+$, 97.33%.

Note: Traces of TFA remained with the product.

Neutralization of TFA impurities from *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

tert-Butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-2,2,2-trifluoroacetic acid (0.29 g, 0.833 mmol) was dissolved in DCM (25 mL) and washed with aq. $NaHCO_3$ solution (3 x 15 mL). The aqueous layer was extracted with DCM (2 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.140 g, 67.2% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (br s, 1H), 7.56 (t, J = 6.4 Hz, 1H), 5.99 (d, J = 7.0 Hz, 1H), 4.09 (s, 2H), 3.55 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 5.6 Hz, 2H), 1.43 (s, 9H); LCMS (Method G): Rt = 1.26, m/z = 251.1 $[M+H]^+$, 99.74%.

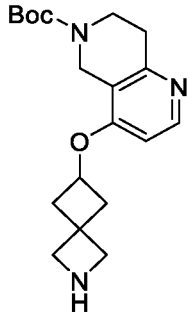
Step 6. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (150 mg, 0.599 mmol) and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (257 mg, 0.719 mmol) in DMF (5 mL), K_2CO_3 (248 mg, 1.798 mmol) was added at RT. The

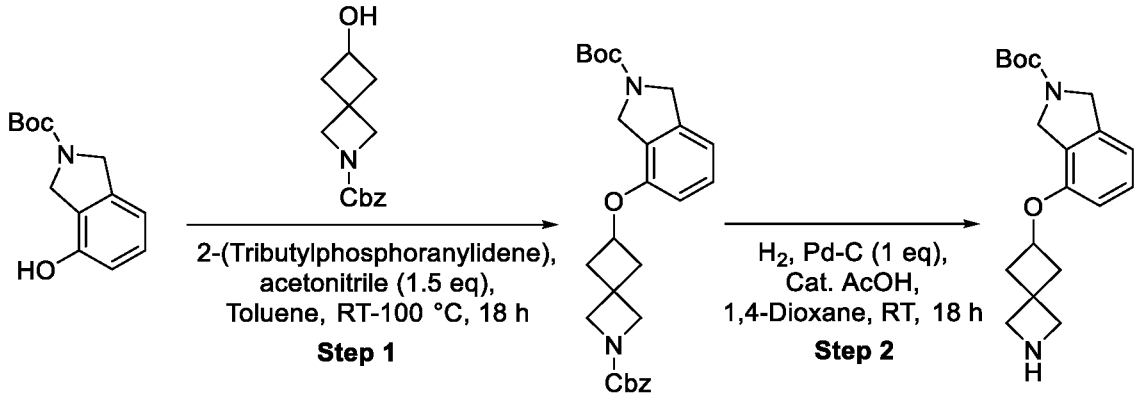
reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (70% EtOAc in hexane). After completion, the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted in 10% MeOH in DCM) to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (250 mg, 80% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 5.6 Hz, 1H), 7.42 - 7.27 (m, 5H), 6.73 (d, J = 5.6 Hz, 1H), 5.02 (s, 2H), 4.81 - 4.69 (m, 1H), 4.36 (s, 2 H), 4.10 - 3.86 (m, 4H), 3.61 (t, J = 5.9 Hz, 2H), 2.82 - 2.75 (m, 4H), 2.31 - 2.16 (m, 2H), 1.42 (s, 9H); LCMS (Method B): Rt = 1.68 min, m/z = 480.3 $[M+H]^+$, 91.79%.

Step 7. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

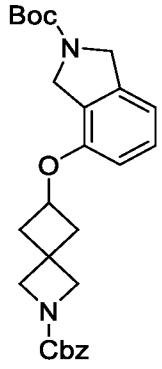


In a 100 mL single neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (230 mg, 0.480 mmol) was added in 2,2,2-trifluoroethanol (5 mL). To this reaction mixture, AcOH (1.44 mg, 0.024 mmol) and Pd-C (100 mg, 0.094 mmol) were added, and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (15 mL). The filtrate was concentrated under reduced pressure to afford *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (160 mg, 79% yield) as a liquid. LCMS (Method D): Rt = 1.45min, m/z = 346.1 $[M+H]^+$, 82.08%.

Intermediate 17. ***tert*-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate**



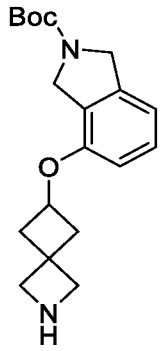
Step 1. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



In a 100 mL round bottom flask under a nitrogen atmosphere, benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (1 g, 4.04 mmol) was added in toluene (15 mL). To this reaction mixture, *tert*-butyl 4-hydroxyisoindoline-2-carboxylate (0.951 g, 4.04 mmol) and 2-(tributylphosphoranylidene) acetonitrile (1.379 g, 6.07 mmol) were added at RT, and the reaction was stirred for 18 h at 100 °C. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to afford the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.6 g, 82% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 - 7.29 (m, 5H), 7.23 (t, J = 7.8 Hz, 1H), 6.89 (dd, J = 5.3, 7.1 Hz, 1H), 6.78 - 6.65 (m, 1H), 5.03 (s, 2H), 4.68 (quin, J = 6.7 Hz, 1H), 4.61 - 4.50 (m, 2H), 4.50 - 4.39 (m, 2H), 4.10 - 3.80 (m, 4H), 2.82 - 2.69 (m, 2H), 2.29 -

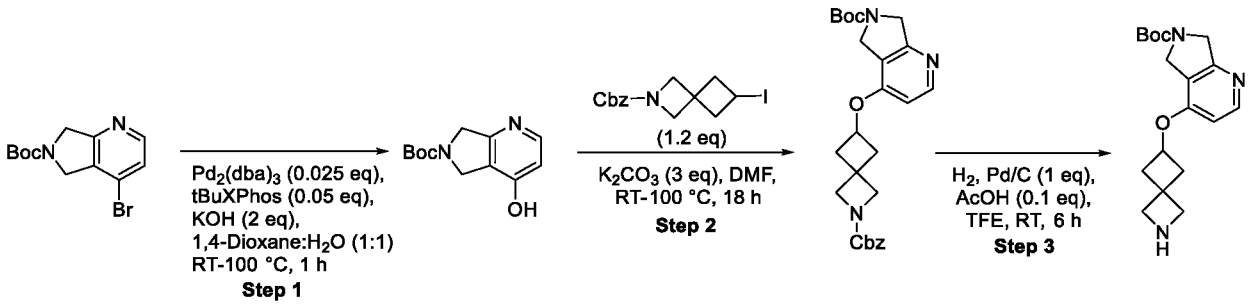
2.15 (m, 2H), 1.46 (s, 9H); LCMS (Method H): Rt = 2.42 min, m/z = 365.1 $[M+H-100]^+$, 95.97%.

Step 2. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate

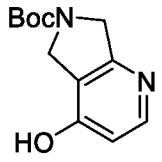


In a 100 mL single neck round bottom flask, *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (600 mg, 1.292 mmol) was added in 1,4-dioxane (5 mL). To this reaction mixture, acetic acid (0.739 µL, 0.013 mmol) and Pd-C (275 mg, 1.292 mmol) were added. The reaction was stirred for 18 h at RT under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 1,4-dioxane (15 mL). The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (350 mg, 73.2% yield) as a viscous liquid. LCMS (Method H): Rt = 1.42 min, m/z = 331.3 $[M+H]^+$, 89.26%. This material was used without further purification.

Intermediate 18. *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



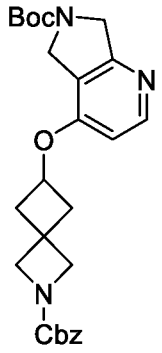
Step 1. tert-Butyl 4-hydroxy-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



Nitrogen was purged through a solution of *tert*-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (300 mg, 1.003 mmol) and KOH (113 mg, 2.006 mmol)

in 1,4-dioxane (5 mL) and water (5 mL) for 5 min. To this solution, *t*BuXPhos (21.29 mg, 0.050 mmol) and $Pd_2(dba)_3$ (22.96 mg, 0.025 mmol) were added at RT. The reaction was stirred at 100 °C for 1 h and monitored by TLC (10% MeOH in DCM). The reaction was diluted with saturated ammonium chloride (10 mL) and extracted with 10% MeOH in DCM (4 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude material. The quantity obtained from the organic layer was minimal (13 mg). Therefore, the aqueous layer was concentrated under reduced pressure to obtain the crude product as a solid. To this solid, 50% MeOH in DCM (25 mL) was added, and the mixture was filtered and washed with 50% MeOH in DCM (25 mL). The combined organic layer was concentrated under reduced pressure to obtain the crude compound. The crude was triturated with 50% EtOAc in hexane (25 mL), and the organic layer was decanted. The solid was dried under reduced pressure to obtain *tert*-butyl 4-hydroxy-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (230 mg, 85% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, J = 6.2 Hz, 1H), 6.27 (d, J = 6.2 Hz, 1H), 4.51 – 4.28 (m, 4H), 1.45 (s, 9H), -OH proton is merged with solvent peak; LCMS (Method D): Rt = 1.09 min, m/z = 237.2 $[M+H]^+$; 87.20%.

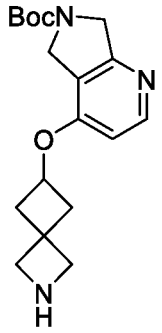
Step 2. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



In a 25 mL pressure vial, *tert*-butyl 4-hydroxy-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (250 mg, 1.058 mmol) and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (454 mg, 1.270 mmol) were added in DMF (5 mL). To this solution, K_2CO_3 (439 mg, 3.17 mmol) was added at RT, and the reaction was stirred at 100 °C for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (480 mg, 86% yield) as a

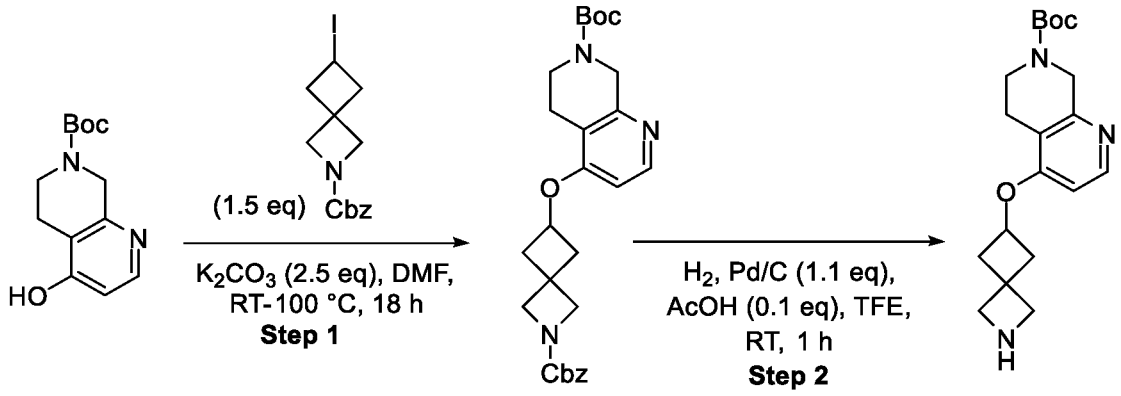
liquid. LCMS (Method B): Rt = 2.51 min, m/z = 466.3 $[M+H]^+$; 87.76%. This material was used without further purification.

Step 3. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate

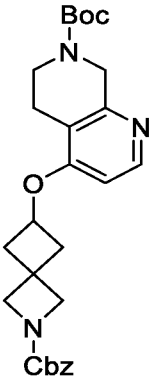


In a 25 mL round bottom flask, *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (480 mg, 1.031 mmol) was added in 2,2,2-trifluoroethanol (10 mL). To this solution, AcOH (5.90 µL, 0.103 mmol) and Pd-C (219 mg, 1.031 mmol) were added, and the reaction was stirred at RT for 6 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (100% EtOAc). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (350 mg, 90% yield) as a solid. LCMS (Method B): Rt = 1.31 min, m/z = 332.4 $[M+H]^+$; 87.72%. This material was used without further purification.

Intermediate 19. *tert*-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate

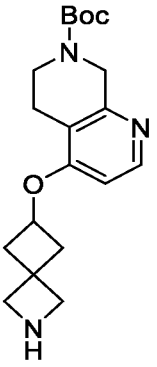


Step 1. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



In a 100 mL round bottom flask, *tert*-butyl 4-hydroxy-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (2.7 g, 10.79 mmol) was added in DMF (25 mL). To this stirred solution, benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (5.78 g, 16.18 mmol) and K_2CO_3 (3.73 g, 27.0 mmol) were added at RT. The reaction was stirred at 100 °C for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (150 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 3% MeOH in DCM) to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (4 g, 71.9% yield) as a sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, J = 5.5 Hz, 1H), 7.42 – 7.28 (m, 5H), 6.71 (d, J = 5.7 Hz, 1H), 5.03 (s, 2H), 4.74 (quin, J = 6.5 Hz, 1H), 4.45 (s, 2H), 4.02 – 3.94 (m, 4H), 3.56 (t, J = 5.9 Hz, 2H), 2.82 – 2.71 (m, 2H), 2.60 (t, J = 5.8 Hz, 2H), 2.29 – 2.19 (m, 2H), 1.42 (s, 9H); LCMS (Method G): Rt = 2.14 min, m/z = 480.4 $[M+H]^+$; 93.29%.

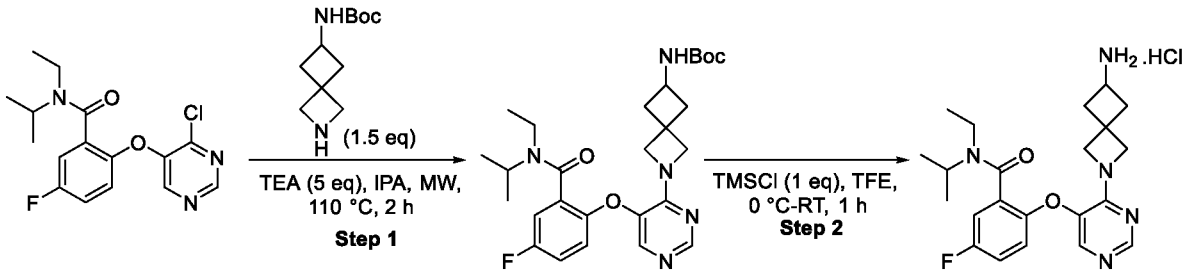
Step 2. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



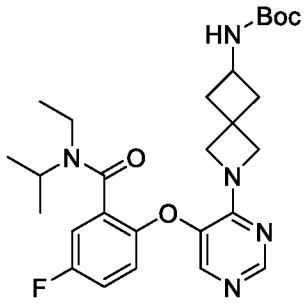
In a 100 mL round bottom flask, a solution of *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (3.023 g, 6.30 mmol) was added in 2,2,2-trifluoroethanol (50 mL). To this solution, acetic acid (0.036 mL, 0.630 mmol) was added, and nitrogen was bubbled through the solution for 10 min. Pd-C (1.476 g, 6.93 mmol) was then added under a nitrogen atmosphere, and the reaction was stirred under a hydrogen atmosphere (balloon pressure) at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM) and LCMS. The reaction was purged with nitrogen gas for 10 min, then filtered through a Celite® pad, and the pad was washed with EtOAc (3 x 100 mL). The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (3.1 g) as a gummy solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 5.5 Hz, 1H), 6.71 (d, J = 5.6 Hz, 1H), 4.69 (p, J = 6.6 Hz, 1H), 4.44 (s, 2H), 3.60 – 3.52 (m, 6H), 2.76 – 2.67 (m, 2H), 2.59 (t, J = 5.8 Hz, 2H), 2.20 – 2.02 (m, 2H), 1.43 (s, 9H); one proton was merged with solvent peaks; LCMS (Method G): Rt = 1.44 min, m/z = 346.2 $[M+H]^+$; 89.64%. This material was used without further purification.

Note: ^{1}HNMR showed a trifluoroethanol solvent impurity peak.

Intermediate 20. 2-((4-(6-Amino-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride



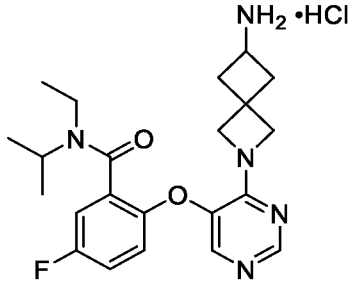
Step 1. tert-Butyl (2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)carbamate



In a 30 mL microwave vial under nitrogen atmosphere, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (400mg, 1.184 mmol) was added in IPA (5

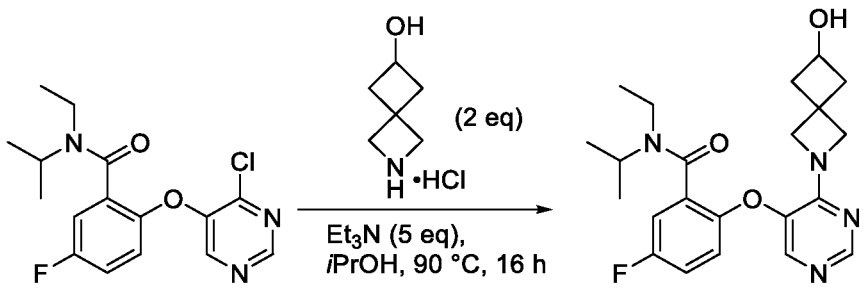
mL) at RT. To this solution, TEA (0.832 mL, 5.92 mmol) and *tert*-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate (377 mg, 1.776 mmol) were added. The reaction was irradiated at 110 °C in the microwave for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to RT and concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5-10% MeOH in DCM) to obtain *tert*-butyl (2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)carbamate (600 mg, 85% yield) as a semi-solid. LCMS (Method D): Rt = 1.92 min, m/z = 514.1 $[M+H]^+$, 86.88%.

Step 2. 2-((4-(6-Amino-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



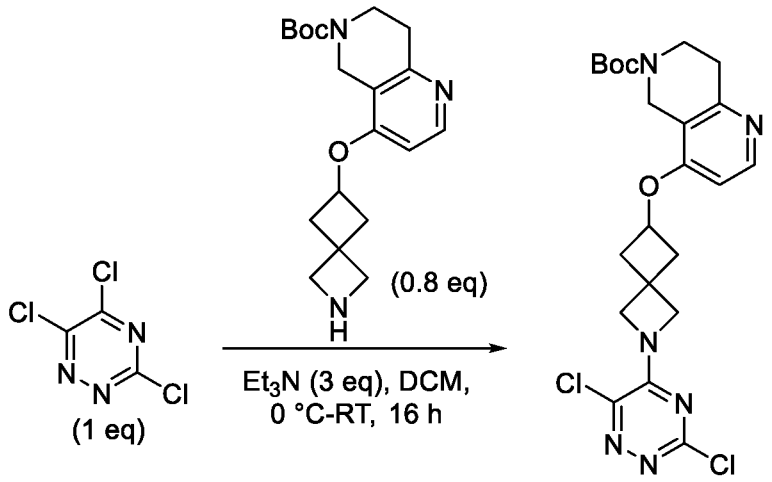
To a stirred solution of *tert*-butyl (2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)carbamate (600 mg, 1.168 mmol) in 2,2,2-trifluoroethanol (6 mL), TMSCl (0.593 mL, 4.67 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain 2-((4-(6-amino-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (480 mg, 82% yield) as a solid. LCMS (Method D): Rt = 1.36 min, m/z = 414.2 $[M+H]^+$, 83.57%.

Intermediate 21. *N*-Ethyl-5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide



To a stirred solution of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (1.0 g, 2.96 mmol) in 2-propanol (10 mL), Et_3N (2.063 mL, 14.80 mmol) and 2-azaspiro[3.3]heptan-6-ol hydrochloride (0.886 g, 5.92 mmol) were added at RT. The reaction was stirred for 16 h at 90 °C. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 10% MeOH in DCM) to afford *N*-ethyl-5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (1.055 g, 85.97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36 - 8.20 (m, 1H), 7.80 - 7.61 (m, 1H), 7.36 - 7.17 (m, 2H), 7.13 - 6.92 (m, 1H), 5.04 (d, J = 6.3 Hz, 1H), 4.20 - 3.84 (m, 6H), 3.81 – 3.67 (m, 1H), 2.44 - 2.41 (m, 2H), 2.00 - 1.86 (m, 2H), 1.28 - 0.93 (m, 9H) one proton merged with moisture peak; LCMS (Method D): Rt = 1.53 min, m/z = 415.2 $[M+H]^+$, 85.98%.

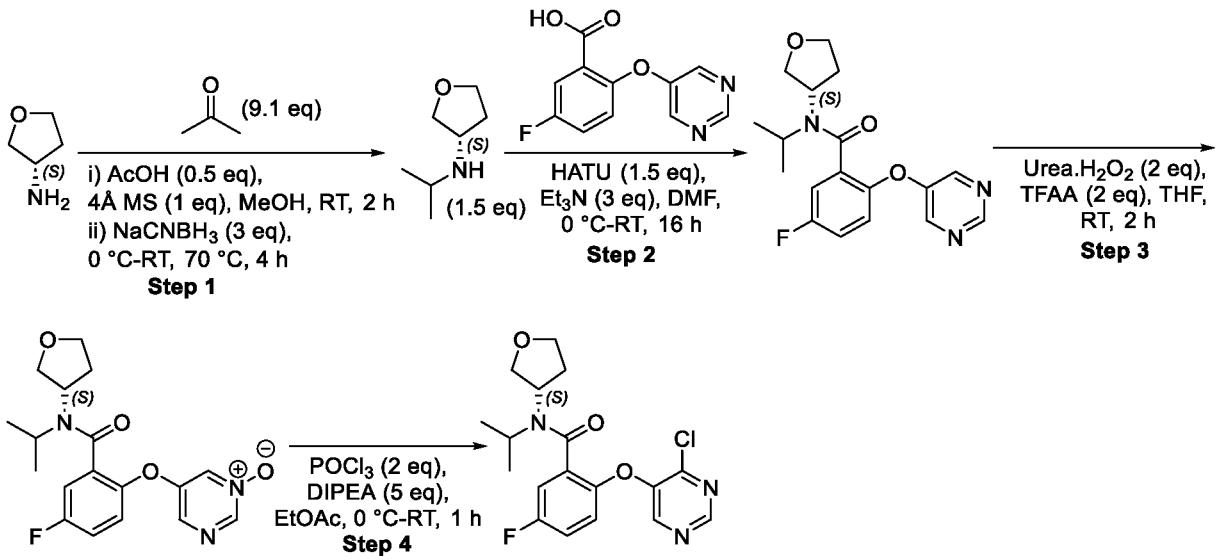
Intermediate 22. *tert*-Butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



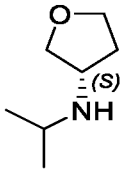
To a stirred solution of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.49 g, 4.34 mmol) in DCM (30 mL), Et_3N (2.268 mL, 16.27 mmol) was added at 0 °C under nitrogen atmosphere. To this reaction mixture, 3,5,6-trichloro-1,2,4-triazine (1 g, 5.42 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 80% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.5 g, 55.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 5.6Hz, 1H), 6.75 (d, J

= 5.6 Hz, 1H), 4.85 - 4.72 (m, 3H), 4.41 - 4.35 (m, 2H), 4.28 - 4.17 (m, 2H), 3.63 (br t, *J* = 5.8 Hz, 2H), 2.87 - 2.79 (m, 4H), 2.38 - 2.32 (m, 2H), 1.43 (s, 9H); LCMS (Method B): Rt = 2.06 min, m/z = 493.3 $[M]^+$, 495.2 $[M+2]^+$, 99.14%.

Intermediate 23. (*S*)-2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide

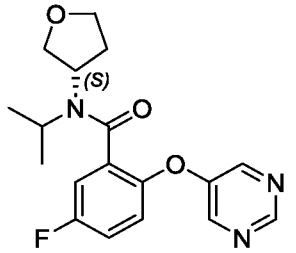


Step-1. (S)-N-Isopropyltetrahydrofuran-3-amine



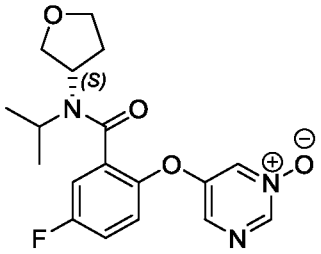
To a stirred solution of (*S*)-tetrahydrofuran-3-amine (3.0 g, 34.4 mmol) and acetone (23.21 mL, 313 mmol) in MeOH (30 mL), acetic acid (0.985 mL, 17.22 mmol) and molecular sieves (4Å) (3.0 g, 34.4 mmol) were added at RT. The reaction was stirred at RT for 2 h. The reaction was cooled to 0 °C, and sodium cyanoborohydride (6.49 g, 103 mmol) was added. The reaction was slowly warmed RT and stirred at 70 °C for 4 h. After completion, the reaction was cooled to RT and filtered through a Celite® pad, and the pad was washed with EtOAc (3 x 50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (50 mL). The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain (*S*)-*N*-isopropyltetrahydrofuran-3-amine (1.7 g, 33.3% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81 - 3.70 (m, 2 H), 3.68 - 3.59 (m, 1 H), 3.50 - 3.35 (m, 3 H), 2.90 - 2.79 (m, 1 H), 2.08-1.96 (m, 1 H), 1.70 - 1.58 (m, 1 H), 1.04-0.97 (m, 6 H); ELSD (Method D): Rt = 0.45 min, m/z = 130.2 $[M+H]^+$, 87.63%. This material was used without further purification.

Step 2. (S)-5-Fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)-N-(tetrahydrofuran-3-yl)benzamide



To a stirred solution of 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (1.0 g, 4.27 mmol) in DMF (5 mL), TEA (1.786 mL, 12.81 mmol) and HATU (2.435 g, 6.41 mmol) were added at 0 °C. To this reaction mixture, (*S*)-*N*-isopropyltetrahydrofuran-3-amine (0.828 g, 6.41 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (80% EtOAc in hexane). After completion, the reaction was quenched with cold water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using EtOAc and hexane (product was eluted at 70% EtOAc in hexane) to obtain (*S*)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(tetrahydrofuran-3-yl)benzamide (1.0 g, 51.3% yield) as a liquid. LCMS (Method D): Rt = 1.47 min, m/z = 346.3 $[M+H]^+$, 75.73%.

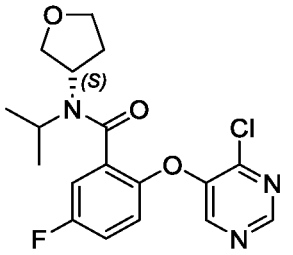
Step 3. (S)-5-(4-Fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidine 1-oxide



To a stirred solution of (*S*)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(tetrahydrofuran-3-yl)benzamide (1.0 g, 2.90 mmol) in THF (10 mL), urea hydrogen peroxide (0.545 g, 5.79 mmol) was added at 0 °C. TFAA (0.818 mL, 5.79 mmol) was added to this reaction mixture, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (100% EtOAc in hexane). After completion, the reaction was quenched with sodium bicarbonate solution (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with saturated sodium thiosulfate solution (3 x 25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain (*S*)-5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidine 1-oxide (900

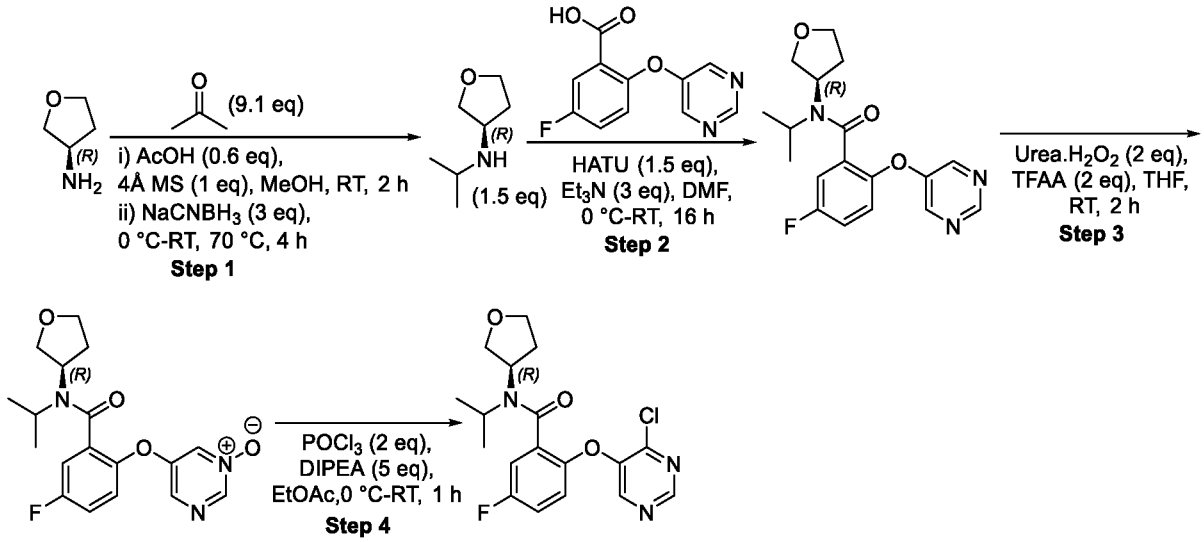
mg, 64.4% yield) as a semi-solid. LCMS (Method D): Rt = 1.32 min, m/z = 362.3 $[M+H]^+$, 74.82%. This material was used without further purification.

Step 4. (S)-2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydrofuran-3-yl)benzamide

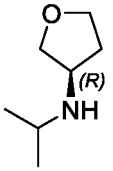


To a stirred solution of (*S*)-5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidine 1-oxide (900 mg, 2.490 mmol) in EtOAc (10 mL), DIPEA (2.175 mL, 12.45 mmol) was added. $POCl_3$ (0.464 mL, 4.98 mmol) was slowly added to this reaction mixture at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain (*S*)-2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide (225 mg, 19.05% yield) as a semi-solid. LCMS (Method D): Rt = 1.81 min, m/z = 380.1 $[M+H]^+$, 80.10%.

Intermediate 24. (*R*)-2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide



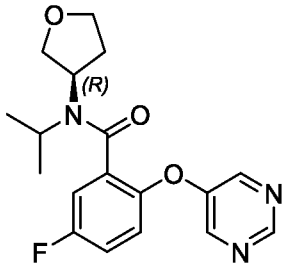
Step 1. (R)-N-Isopropyltetrahydrofuran-3-amine



This compound was synthesized following the procedure described for the synthesis of Intermediate 23, step 1, starting with acetone and 1 equivalent of (*R*)-tetrahydrofuran-3-amine, except that 0.6 equivalent of acetic acid was used to obtain crude (*R*)-*N*-isopropyltetrahydrofuran-3-amine as a semi-solid.

Yield: 55.2%; ^{1}H NMR (400 MHz, DMSO) δ 3.81 - 3.68 (m, 2H), 3.69 - 3.59 (m, 1H), 3.52 - 3.35 (m, 1H), 2.90 - 2.80 (m, 1H), 2.07 - 1.96 (m, 1H), 1.72 - 1.59 (m, 1H), 1.15 - 1.08 (m, 2H), 1.05 - 0.97 (m, 6H). This material was used without further purification.

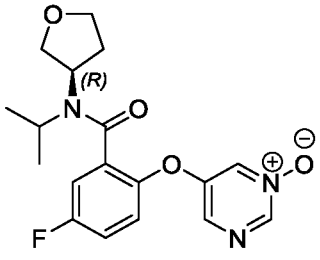
Step 2. (R)-5-Fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)-N-(tetrahydrofuran-3-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 23, step 2, starting with 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid, except that 1.5 equivalents of (*R*)-*N*-isopropyltetrahydrofuran-3-amine was used. The crude was purified by silica gel flash column chromatography using EtOAc and hexane (product was eluted at 50-70% EtOAc in hexane) to obtain (*R*)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(tetrahydrofuran-3-yl)benzamide as semi-solid.

Yield: 52.3%; LCMS (Method B): Rt 2.02 min, m/z = 346.2 $[M+H]^+$, 77.16%.

Step 3. (R)-5-(4-Fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidine 1-oxide

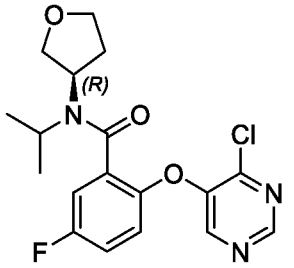


This compound was synthesized following the procedure described for the synthesis of Intermediate 23, step 3, starting with (*R*)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-

(tetrahydrofuran-3-yl)benzamide to obtain (*R*)-5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidine 1-oxide as a semi-solid.

Yield: 59.8%; LCMS (Method B): Rt = 1.83 min, m/z = 362.2 $[M+H]^+$, 81.71%. This material was used without further purification.

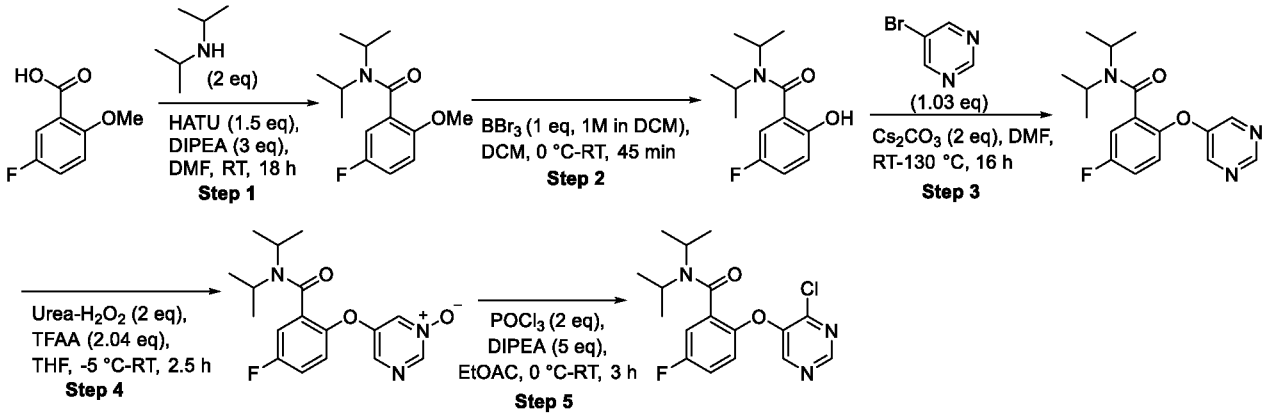
Step 4. (R)-2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydrofuran-3-yl)benzamide



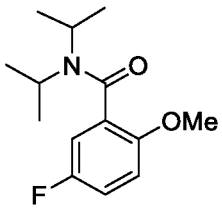
This compound was synthesized following the procedure described for the synthesis of Intermediate 23, step 4, starting with (*R*)-5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidine 1-oxide. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 30-40% EtOAc in hexane) to obtain (*R*)-2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide as a semi-solid.

Yield: 20.28%; LCMS (Method D): Rt = 1.68 min, m/z = 380.2 $[M+H]^+$, 81.10%.

Intermediate 25. 2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

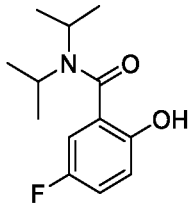


Step 1. 5-Fluoro-N,N-diisopropyl-2-methoxybenzamide



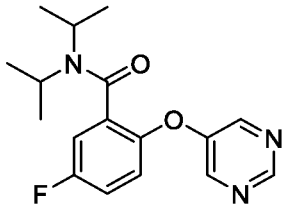
In a dried, 2 L four neck round bottom flask under a nitrogen atmosphere, 5-fluoro-2-methoxybenzoic acid (46 g, 270 mmol) was added in DMF (460 mL). To this solution, diisopropylamine (77 mL, 541 mmol), DIPEA (142 mL, 811 mmol), and HATU (154 g, 406 mmol) were added at 0 °C. The reaction was stirred at RT for 18 h. The reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (2 L) and extracted with 10% EtOAc in hexane (2 x 2 L). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 5-fluoro-*N*,*N*-diisopropyl-2-methoxybenzamide (66 g, 94% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21 - 7.12 (m, 1H), 7.09 - 7.03 (m, 1H), 6.98 (dd, J = 3.1, 8.3 Hz, 1H), 3.76 (s, 3H), 3.60 - 3.44 (m, 2H), 1.42 (t, J = 6.8 Hz, 6H), 1.10 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H); LCMS (Method H): Rt = 2.00 min, m/z = 254.2 $[M+H]^+$; HPLC (Method A): Rt = 6.08 min, 97.06%.

Step 2. 5-Fluoro-2-hydroxy-N,N-diisopropylbenzamide



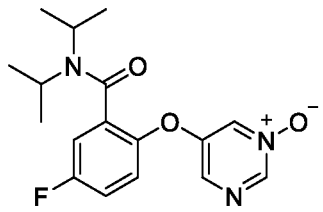
To a stirred solution of 5-fluoro-*N*,*N*-diisopropyl-2-methoxybenzamide (25 g, 99 mmol) in DCM (500 mL), BBr_3 (99 mL, 99 mmol, 1M in DCM) in DCM was added slowly at 0 °C under a nitrogen atmosphere. The reaction was slowly warmed to RT and stirred for 45 min. The progress of the reaction was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with ice-cold water (400 mL), and extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine solution (200 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide (23.7 g, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 - 8.42 (m, 1H), 7.06 - 6.99 (m, 1H), 6.99 - 6.94 (m, 1H), 6.88 (dd, J = 3.0, 8.6 Hz, 1H), 1.41 (d, J = 6.8 Hz, 12H); LCMS (Method H): Rt = 1.77 min, m/z = 240.4 $[M+H]^+$; 99.72%. This material was used without further purification.

Step 3. 5-Fluoro-N,N-diisopropyl-2-(pyrimidin-5-yloxy)benzamide



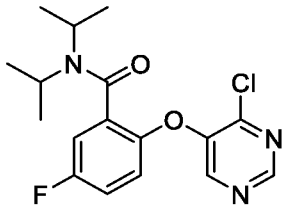
In a dried, 1 L four neck round bottom flask under a nitrogen atmosphere, 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide (25 g, 104 mmol) was added in DMF (250 mL). To this solution, Cs_2CO_3 (68.1 g, 209 mmol) and 5-bromopyrimidine (17.11 g, 108 mmol) were added at RT. The reaction was stirred at 130 °C for 16 h. The progress of the reaction was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (400 mL) and extracted with EtOAc (3 x 400 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 24% EtOAc in hexane) to obtain 5-fluoro-*N*,*N*-diisopropyl-2-(pyrimidin-5-yloxy)benzamide (16.3 g, 46.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.51 (s, 2H), 7.39 - 7.28 (m, 3H), 3.67 (spt, *J* = 6.6 Hz, 1H), 3.57 - 3.43 (m, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); LCMS (Method H): Rt = 1.82 min, m/z = 318.4 $[M+H]^+$; 95.35%.

Step 4. 5-(2-(Diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide



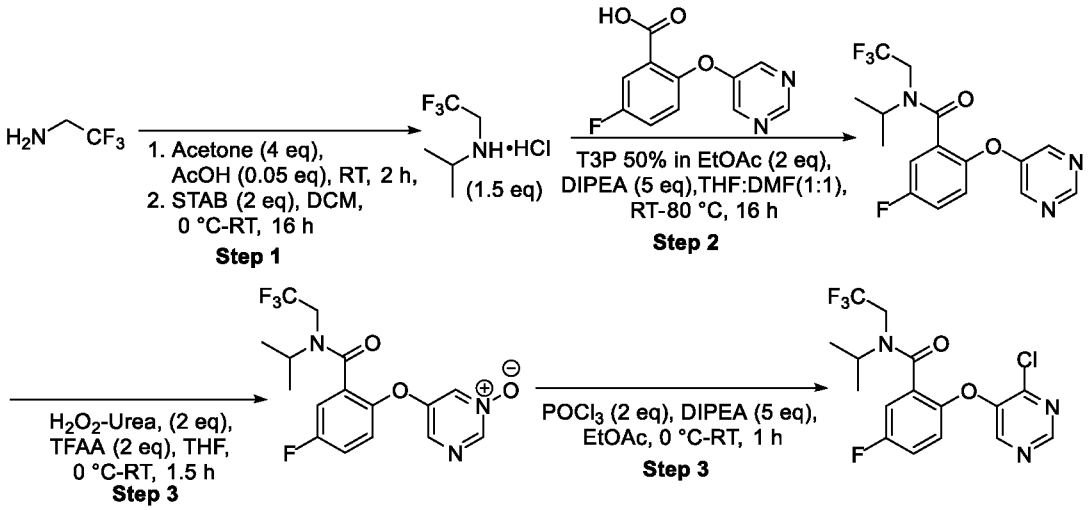
To a stirred solution of 5-fluoro-*N*,*N*-diisopropyl-2-(pyrimidin-5-yloxy)benzamide (16 g, 50.4 mmol) in THF (170 mL), urea hydrogen peroxide (9.49 g, 101 mmol) was added, and then, TFAA (14.53 mL, 103 mmol) was added dropwise over 30 min at -5 °C. The reaction was allowed to stir at RT for 2 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was quenched with saturated sodium thiosulfate solution (100 mL) and then saturated ammonium carbonate solution (100 mL). The mixture was extracted with EtOAc (2 x 200 mL), and the organic layer was washed with brine solution (100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was washed with *n*-heptane (2 x 100 mL) to obtain crude 5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (16 g, 80% yield) as a solid. LCMS (Method A): Rt = 1.76 min, m/z = 334.3 $[M+H]^+$; HPLC (Method A): Rt = 4.82 min, 79.44%. This material was used without further purification.

Step 5. 2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide

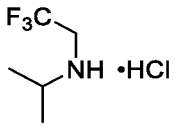


In a dried, 500 mL two neck round bottom flask under a nitrogen atmosphere, 5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (16 g, 48.0 mmol) was added in EtOAc (160 mL). To this solution, DIPEA (41.8 mL, 240 mmol) and $POCl_3$ (8.97 mL, 96 mmol) were added at 0 °C, and the reaction was stirred at 0 °C for 30 min. The reaction was allowed to stir at RT for 2.5 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). The reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 30% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (9 g, 51.2% yield) as a solid). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (s, 1H), 8.23 (s, 1H), 7.16 - 7.09 (m, 1H), 7.09 - 7.00 (m, 2H), 3.78 (spt, J = 6.7 Hz, 1H), 3.51 (spt, J = 6.8 Hz, 1H), 1.51 (d, J = 6.8 Hz, 3H), 1.36 (d, J = 6.9 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H); LCMS (Method H): Rt = 2.08 min, m/z = 352.4 $[M+H]^+$; 96.76%.

Intermediate 26. 2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide

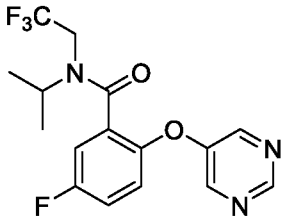


Step 1. N-(2,2,2-Trifluoroethyl)propan-2-amine hydrochloride



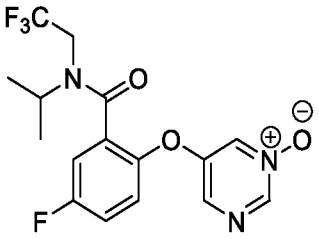
In a 2 L two neck round bottom flask under a nitrogen atmosphere, 2,2,2-trifluoroethan-1-amine (25 g, 252 mmol) was added in DCM (350 mL) at RT. To this solution, acetone (65.1 mL, 1010 mmol) and AcOH (0.722 mL, 12.62 mmol) were added, and the reaction was stirred at RT for 2 h. The reaction was cooled to 0 °C, and sodium triacetoxyborohydride (107 g, 505 mmol) was added. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (500 mL) and extracted with DCM (3 x 200 mL). The combined organic layer was dried over sodium sulfate and filtered. To the filtrate, 4M HCl in 1,4-dioxane (40 mL) was added, and the reaction was stirred at RT. After 30 min, the solvent was evaporated under reduced pressure to obtain crude *N*-(2,2,2-trifluoroethyl)propan-2-amine hydrochloride (39 g, 87% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (br s, 2H), 4.13 - 3.92 (m, 2H), 3.48 - 3.34 (m, 1H), 1.31 (d, J = 6.6 Hz, 6H). This material was used without further purification.

Step 2. 5-Fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)-N-(2,2,2-trifluoroethyl)benzamide



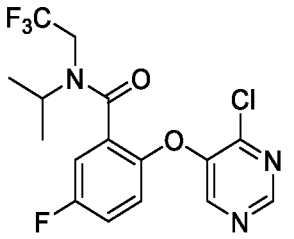
To a stirred solution of 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (1 g, 4.27 mmol) in DMF (5 mL):THF (5 mL), DIPEA (3.73 mL, 21.35 mmol) and propanephosphonic acid anhydride (5.45 mL, 8.54 mmol, 50 wt % in EtOAc) were added at RT. To this reaction mixture, *N*-(2,2,2-trifluoroethyl)propan-2-amine hydrochloride (1.138 g, 6.41 mmol) was added, and the reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (40 % EtOAc in hexane). After completion, the reaction was cooled to RT, quenched with water (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 40% EtOAc in hexane) to obtain 5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(2,2,2-trifluoroethyl)benzamide (900 mg, 55.0% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.34 (s, 2H), 7.48 - 7.38 (m, 3H), 4.32 - 4.09 (m, 2H), 3.94 - 3.84 (m, 1H), 1.12 (br d, J = 6.3 Hz, 6H); LCMS (Method B): Rt = 2.24 min, m/z = 358.2 $[M+H]^+$, 93.23%.

Step 3. 5-(4-Fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidine 1-oxide



To a stirred solution of 5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(2,2,2-trifluoroethyl)benzamide (900 mg, 2.52 mmol) in THF (10 mL), urea hydrogen peroxide (0.545 g, 5.79 mmol) was added at 0 °C. To this reaction mixture, TFAA (0.712 mL, 5.04 mmol) was added, and the reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with sodium bicarbonate solution (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with saturated sodium thiosulfate solution (3 x 25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidine 1-oxide (804 mg, 81% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.88 (d, J = 1.2 Hz, 1H), 8.43 (s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.51 - 7.39 (m, 3H), 4.34 - 4.11 (m, 2H), 3.95 - 3.83 (m, 1H), 1.09 (br s, 6H); LCMS (Method B): Rt = 2.16 min, m/z = 374.3 $[M+H]^+$, 94.68%. This material was used without further purification.

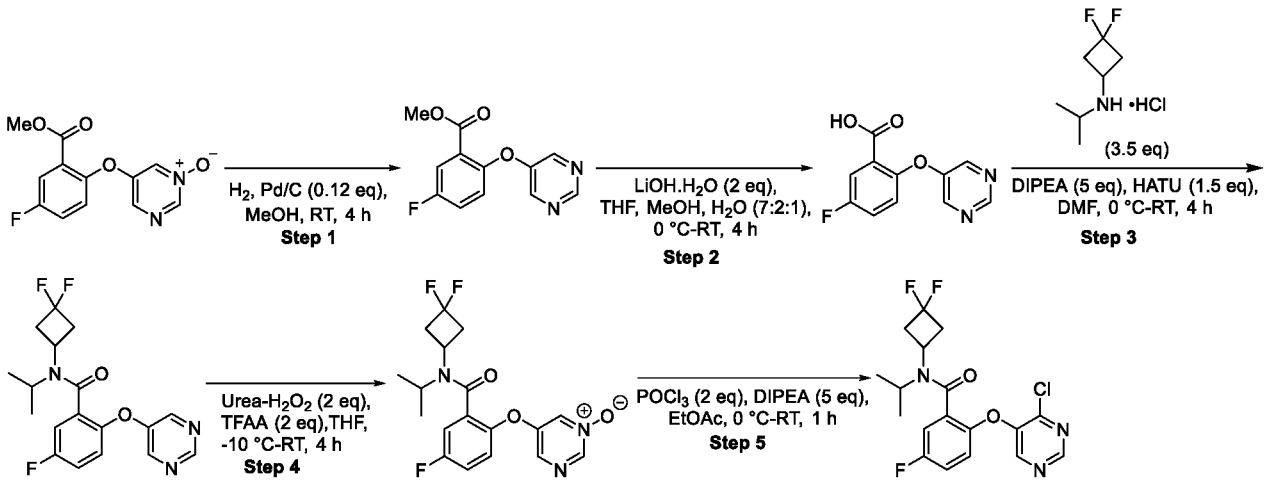
Step 4. 2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



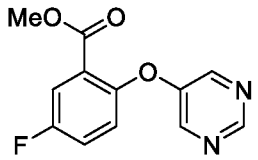
To a stirred solution of 5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidine 1-oxide (800 mg, 2.143 mmol) in EtOAc (10 mL), DIPEA (1.871 mL, 10.72 mmol) was added at 0 °C. To this reaction mixture, $POCl_3$ (0.399 mL, 4.29 mmol) was added dropwise at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 40-60% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-

trifluoroethyl)benzamide (600 mg, 71.1% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.52 (s, 1H), 7.44 - 7.35 (m, 3H), 4.32 - 4.08 (m, 1H), 3.93 - 3.85 (m, 2H), 1.13 - 1.02 (m, 6H); LCMS (Method C): Rt = 2.15 min, m/z = 392.0 $[M+H]^+$, 99.47%.

Intermediate 27. 2-((4-Chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide



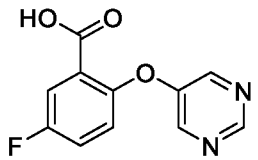
Step 1. Methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate



Step 1 was performed following the same procedure in two batches, 2 x 20 g batches.

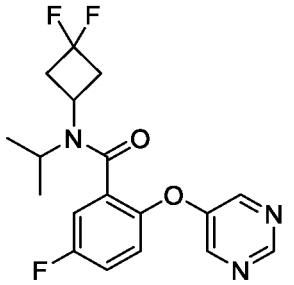
In a dried, 1 L two-neck round bottom flask under a nitrogen atmosphere, 5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidine 1-oxide (20 g, 76 mmol) was added in MeOH (400 mL). To this solution, Pd/C (9.67 g, 9.08 mmol) was added, and the reaction was stirred at RT for 4 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction mixtures from the two batches were combined and filtered through a Celite® pad, and the pad was washed with MeOH (2 x 500 mL). The filtrate was concentrated under reduced pressure to obtain crude methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (40 g, 79% combined yield) as a solid. LCMS (Method G): Rt = 1.63 min, m/z = 249.1 $[M+H]^+$; 74.48%. This material was used without further purification.

Step 2. 5-Fluoro-2-(pyrimidin-5-yloxy)benzoic acid



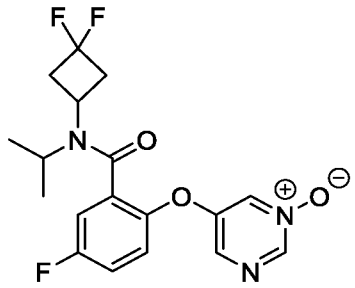
In a dried, 1 L round bottom flask under a nitrogen atmosphere, methyl 5-fluoro-2-(pyrimidin-5-yloxy)benzoate (40 g, 161 mmol) was added in a mixture of THF (280 mL), MeOH (80 mL) and water (40 mL). To this solution, $LiOH.H_2O$ (13.54 g, 322 mmol) was added at 0 °C, and the reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. Water (150 mL) was added to the residue and washed with EtOAc (2 x 200 mL). The aqueous layer was acidified with HCl (1.5 N), and the solid was filtered. The solid compound was dried by azeotropic removal of water with toluene under reduced pressure to afford crude 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (31 g, 81% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.41 (br s, 1H), 8.92 (s, 1H), 8.47 (s, 2H), 7.70 (dd, J = 3.3, 8.8 Hz, 1H), 7.56 (ddd, J = 3.3, 7.9, 8.8 Hz, 1H), 7.41 (dd, J = 4.6, 9.0 Hz, 1H); LCMS (Method B): Rt = 1.27 min, m/z = 235.2 $[M+H]^+$; 98.20%. This material was used without further purification.

Step 3. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)benzamide



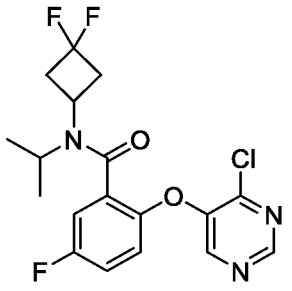
To a stirred solution of 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (4.3 g, 17.91 mmol) in DMF (5 mL), DIPEA (15.98 mL, 90 mmol), HATU (10.21 g, 26.9 mmol) and 3,3-difluoro-*N*-isopropylcyclobutan-1-amine hydrochloride (11.64 g, 62.7 mmol) were added at 0 °C. The reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC (20% EtOAc in hexane). After completion, the reaction was diluted with ice-cold water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine solution (500 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 80% EtOAc in hexane) to obtain *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (3.2 g, 46.0% yield) as an oil. LCMS (Method B): Rt = 1.74 min, m/z = 366.2 $[M+H]^+$; 94.38%.

Step 4. 5-(2-((3,3-Difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide



In a dried, 250 mL two neck round bottom flask under a nitrogen atmosphere, *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (3.2 g, 8.76 mmol) was added in THF (10 mL). To this solution, urea hydrogen peroxide (1.648 g, 17.52 mmol) and TFAA (2.486 mL, 17.52 mmol) were added at -10 °C. The reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC (100% EtOAc in hexane). After completion, the reaction was quenched with saturated sodium bicarbonate solution (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with 1M $Na_2S_2O_3$ solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (3.4 g, 68.2% yield) as a viscous liquid. LCMS (Method B): Rt = 1.72 min, m/z = 382.2 $[M+H]^+$; 67.07%. This material was used without further purification.

Step 5. 2-((4-Chloropyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

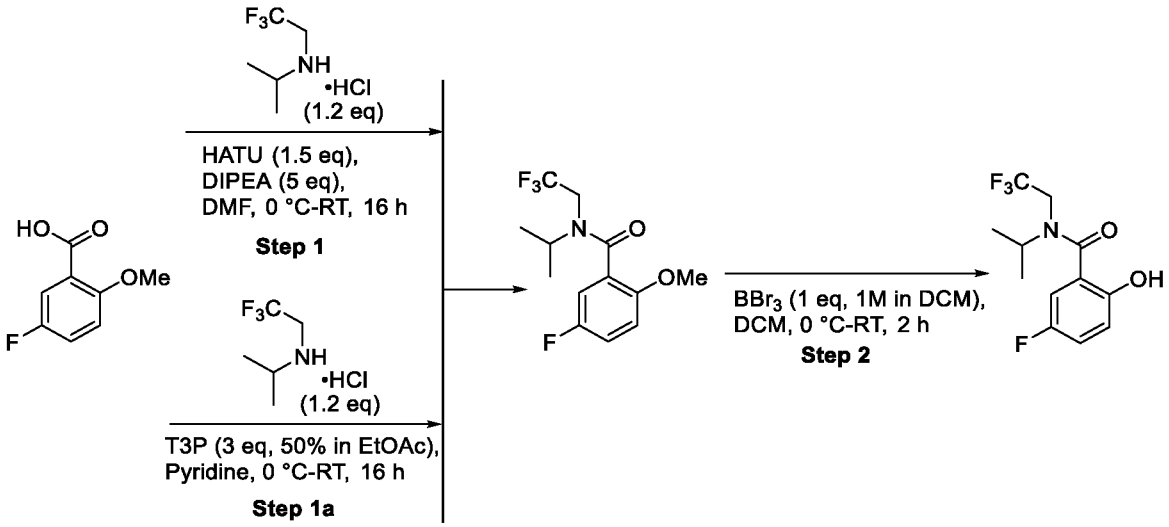


Step 5 was performed following the same procedure in two batches, 2 x 1.6 g batches.

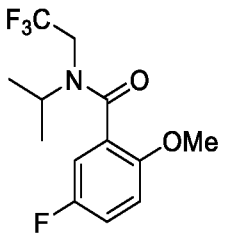
In a dried, 100 mL two neck round bottom flask under a nitrogen atmosphere, 5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (1.6 g, 4.20 mmol) was added in EtOAc (15 mL). To this solution, DIPEA (3.74 mL, 20.98 mmol) and $POCl_3$ (0.784 mL, 8.39 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (40% EtOAc in hexane). After completion,

the reaction mixtures from the two batches were combined and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography by using EtOAc in hexane (product eluted at 50% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (1.5 g, 77% combined yield) as a semi-solid. LCMS (Method B): Rt = 2.06 min, m/z = 400.2 $[M+H]^+$; 86.58%.

Intermediate 28. 5-Fluoro-2-hydroxy-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide



Step 1. 5-Fluoro-N-isopropyl-2-methoxy-N-(2,2,2-trifluoroethyl)benzamide

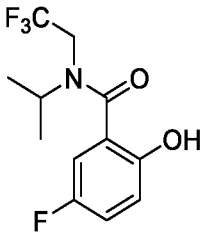


To a stirred solution of 5-fluoro-2-methoxybenzoic acid (5 g, 29.4 mmol) in DMF (50 mL), *N*-(2,2,2-trifluoroethyl)propan-2-amine hydrochloride (6.26 g, 35.3 mmol) was added at RT under a nitrogen atmosphere. To this solution, HATU (16.76 g, 44.1 mmol) and DIPEA (25.6 mL, 147 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h, and the reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with ice-cold water (50 mL) and brine solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 10-30% EtOAc in hexane) to obtain 5-fluoro-*N*-isopropyl-2-methoxy-*N*-(2,2,2-trifluoroethyl)benzamide (3 g, 33.9% yield) as a solid. LCMS (Method G): Rt = 2.09 min, m/z = 294.1 [M+H]+; 97.25%.

Step 1a. 5-Fluoro-N-isopropyl-2-methoxy-N-(2,2,2-trifluoroethyl)benzamide

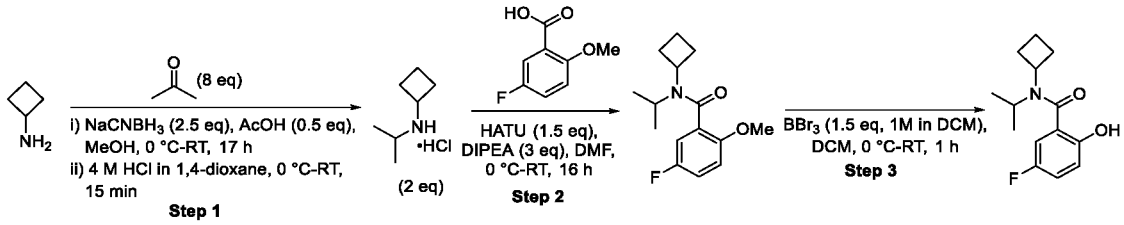
To a stirred solution of 5-fluoro-2-methoxybenzoic acid (5 g, 29.4 mmol) in pyridine (50 mL), *N*-(2,2,2-trifluoroethyl)propan-2-amine hydrochloride (6.26 g, 35.3 mmol) was added at 0 °C under a nitrogen atmosphere. T3P (52.5 mL, 88 mmol, 50 wt % in EtOAc) was added to this solution at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). The reaction was quenched with ice-cold water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with ice-cold water (100 mL) and brine solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted in 20% EtOAc in hexane) to obtain 5-fluoro-*N*-isopropyl-2-methoxy-*N*-(2,2,2-trifluoroethyl)benzamide (4.3 g, 49.4 % yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (dt, J = 3.0, 8.7 Hz, 1H), 7.16 - 7.06 (m, 2H), 4.32 - 4.13 (m, 2H), 3.79 - 3.78 (s, 3H), 3.75 - 3.65 (m, 1H), 1.32 - 1.03 (m, 6H); LCMS (Method G): Rt = 2.25 min, m/z = 294.1 [M+H]+; 99.13%.

Step 2. 5-Fluoro-2-hydroxy-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide

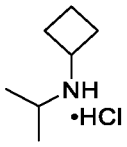


In a dried, 500 mL two neck round bottom flask under a nitrogen atmosphere, 5-fluoro-*N*-isopropyl-2-methoxy-*N*-(2,2,2-trifluoroethyl)benzamide (3 g, 10.23 mmol) was dissolved in DCM (60 mL) under a nitrogen atmosphere. BBr3 (10.23 mL, 10.23 mmol, 1M in DCM) was added to this reaction at 0 °C. The reaction was stirred at RT for 2 h. The reaction was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was quenched with water (40 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 5-fluoro-2-hydroxy-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (3 g, 90 % yield) as a solid. LCMS (Method G): Rt = 1.87 min, m/z = 280.1 $[M+H]^+$; 84.83%. This material was used without further purification.

Intermediate 29. ***N*-Cyclobutyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide**

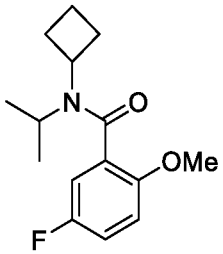


Step 1. N-Isopropylcyclobutanamine hydrochloride



To a solution of cyclobutanamine (1 g, 14.06 mmol) and acetone (8.33 mL, 112 mmol) in MeOH (20 mL), AcOH (0.402 mL, 7.03 mmol) was added at RT. The reaction was stirred for 30 min. To this solution, $NaCNBH_3$ (2.209 g, 35.2 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. To this reaction, 4 M HCl in 1,4 dioxane (300 mL) was added, and the mixture was stirred for 15 min at 0 °C. The reaction was concentrated under reduced pressure to obtain crude *N*-isopropylcyclobutanamine hydrochloride (2 g, 95% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.32 (br s, 2H), 3.79 - 3.67 (m, 1H), 3.21 - 3.09 (m, 1H), 2.23 - 2.28 (m, 2H), 2.21 - 2.10 (m, 2H), 1.84 - 1.69 (m, 2H), 1.21 (d, J = 6.5 Hz, 6H). This material was used without further purification.

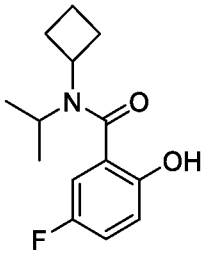
Step 2. N-Cyclobutyl-5-fluoro-N-isopropyl-2-methoxybenzamide



To a stirred solution of 5-fluoro-2-methoxybenzoic acid (1.0 g, 5.88 mmol) in DMF (5 mL), DIPEA (3.14 mL, 17.63 mmol), HATU (3.35 g, 8.82 mmol), and *N*-isopropylcyclobutanamine hydrochloride (1.759 g, 11.76 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was diluted with water (50 mL) extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted in 30% EtOAc in hexane) to obtain *N*-cyclobutyl-5-fluoro-*N*-isopropyl-2-

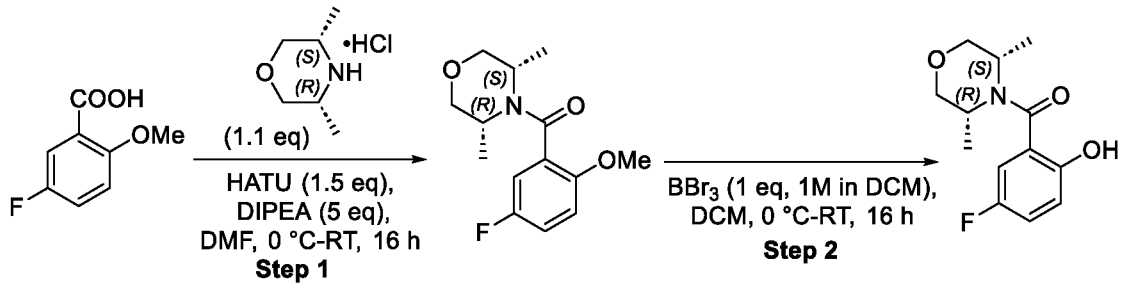
methoxybenzamide (1.3 g, 3.48 mmol, 59.2% yield) as a viscous liquid. LCMS (Method B): Rt = 2.63 min, m/z = 266.2 $[M+H]^+$; 71.48%.

Step 3. N-Cyclobutyl-5-fluoro-2-hydroxy-N-isopropylbenzamide

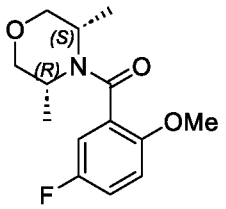


In a dried, 100 mL three-neck round bottom flask under a nitrogen atmosphere, *N*-cyclobutyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide (0.8 g, 3.02 mmol) was added in DCM (20 mL). To this solution, BBr_3 (4.52 mL, 4.52 mmol, 1M in DCM) was added at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (20% EtOAc in hexane). After completion, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with ice-cold water (50 mL) and brine solution (3 x 20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford *N*-cyclobutyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (750 mg, 80% yield) as a sticky solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 7.01 (dt, *J* = 3.3, 8.7 Hz, 1H), 6.89 - 6.79 (m, 2H), 3.95 (quin, *J* = 8.7 Hz, 1H), 3.77 - 3.64 (m, 1H), 2.81 - 2.57 (m, 1H), 2.40 - 2.16 (m, 1H), 2.03 - 1.89 (m, 2H), 1.73 - 1.43 (m, 2H), 1.34 - 1.12 (m, 6H); LCMS (Method B): Rt = 2.44 min, m/z = 252.2 $[M+H]^+$; 81.27%.

Intermediate 30. ((3*S*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone

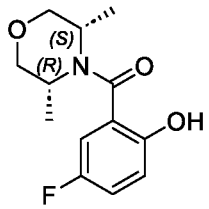


*Step 1. ((3R,5S)-3,5-Dimethylmorpholino)(5-fluoro-2-methoxyphenyl)*methanone



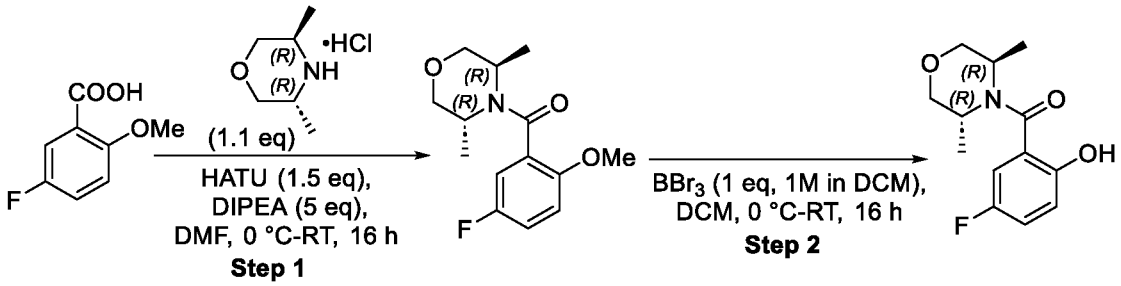
To a stirred solution of 5-fluoro-2-methoxybenzoic acid (5 g, 29.4 mmol) in DMF (50 mL), DIPEA (25.7 mL, 147 mmol) and HATU (16.76 g, 44.1 mmol) were added at 0 °C. To this reaction mixture, (*3R,5S*)-3,5-dimethylmorpholine hydrochloride (4.90 g, 32.3 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (70% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (50 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc and hexane (product was eluted at 30% EtOAc in hexane) to obtain (*3R,5S*)-3,5-dimethylmorpholino)(5-fluoro-2-methoxyphenyl)methanone (5.7 g, 68.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25-7.17 (m, 1H), 7.15-7.06 (m, 2H), 3.78 (s, 3H), 3.76-3.64 (m, 2H), 3.55-3.46 (m, 4H), 1.32-1.06 (br s, 6H); LCMS (Method D): Rt = 1.54 min, m/z = 268.0 $[M+H]^+$, 94.95%.

Step 2. ((3R,5S)-3,5-Dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone

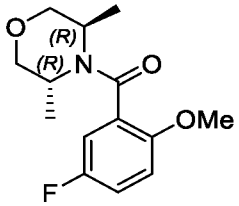


To a stirred solution of (*3R,5S*)-3,5-dimethylmorpholino)(5-fluoro-2-methoxyphenyl)methanone (5.7 g, 21.32 mmol) in DCM (57 mL), BBr_3 (21.32 mL, 19.83 mmol; 1 M in DCM) was added slowly at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (70% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with saturated sodium bicarbonate solution (50 mL), and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude (*3R,5S*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone (5.2 g, 81% yield) as a gummy solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (br s, 1H), 7.07-6.98 (m, 2H), 6.86-6.83 (m, 1H), 3.67-3.65 (m, 2H), 3.51-3.47 (m, 4H), 1.19 (br s, 6H); LCMS (Method D): Rt = 1.29 min, m/z = 254.0 $[M+H]^+$, 84.50%. This material was used without further purification.

Intermediate 31. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone



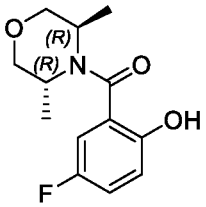
Step 1. (3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-methoxyphenyl)methanone



This compound was synthesized following the procedure described for the synthesis of Intermediate 30, step 1, starting with 5-fluoro-2-methoxybenzoic acid, except that 1.1 equivalent of (3*R*,5*R*)-3,5-dimethylmorpholine hydrochloride was used. The crude was purified by silica gel flash column chromatography using EtOAc and hexane (product was eluted at 30% EtOAc in hexane) to obtain (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-methoxyphenyl)methanone as a semi-solid.

Yield: 65.8%; LCMS (Method D): Rt = 1.52 min, m/z = 268.0 $[M+H]^+$, 97.49%.

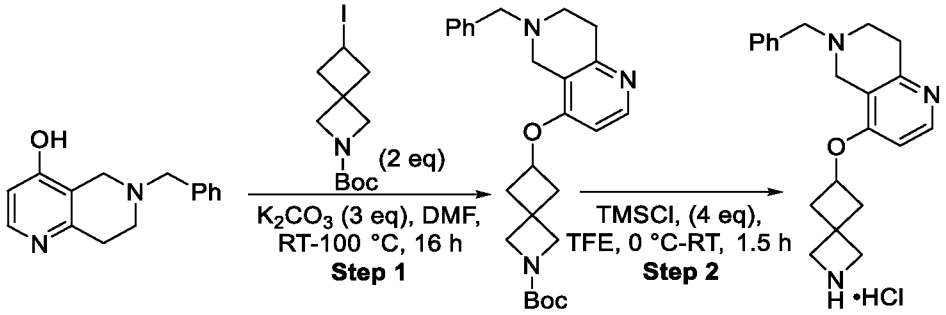
Step 2. (3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone



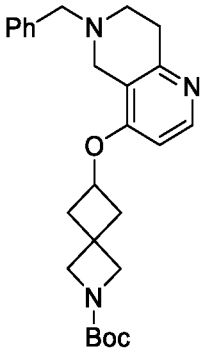
This compound was synthesized following the procedure described for the synthesis of Intermediate 30, step 2, starting with (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-methoxyphenyl)methanone. The crude was purified by silica gel flash column chromatography using EtOAc and hexane (product was eluted at 40% EtOAc in hexane) to obtain (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone as a solid.

Yield: 57.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (br s, 1H), 7.09-6.99 (m, 2H), 6.86-6.83 (m, 1H), 3.86-3.78 (m, Hz, 2H), 3.81 - 3.70 (m, 2H), 3.47-3.44 (m, 2H), 1.21 (d, J = 6.8, 6H); LCMS (Method D): Rt = 1.39 min, m/z; 254.0 $[M+H]^+$, 81.84%.

Intermediate 32. 4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride

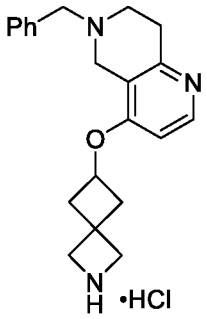


Step 1. tert-Butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



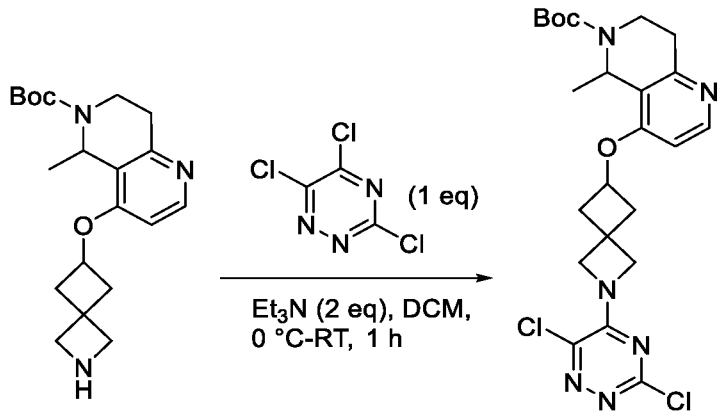
To a stirred solution of 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (104 g, 433 mmol) dissolved in DMF (1000 ml), powdered K_2CO_3 (179 g, 1298 mmol) was added at RT under a nitrogen atmosphere. The reaction was stirred at RT for 5 min. To this solution, *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (280 g, 866 mmol) was added at RT. The resulting mixture was stirred at RT for 10 min and then stirred at 100 °C for 16 h. The reaction was monitored by TLC (100% EtOAc). The reaction was quenched with water (3000 mL) and extracted with EtOAc (4500 mL). The organic layer was washed with cool brine (3 x 4500 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography using 100% EtOAc, and then with 10% MeOH in EtOAc, to afford *tert*-butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (122 g, 64.4 % yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, J = 5.7 Hz, 1H), 7.38 - 7.32 (m, 4H), 7.31 - 7.23 (m, 1H), 6.65 (d, J = 5.5 Hz, 1H), 4.68 (quin, J = 6.7 Hz, 1H), 3.93 - 3.76 (m, 4H), 3.69 (s, 2H), 3.45 (s, 2H), 2.84 - 2.77 (m, 2H), 2.75 - 2.67 (m, 4H), 2.18 - 2.13 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 2.10 min, m/z = 436.2 $[M+H]^+$, 99.49%.

Step 2. 4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



To a stirred solution of *tert*-butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (2 g, 4.59 mmol) in 2,2,2-trifluoroethanol (20 mL), TMSCl (2.347 mL, 18.37 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (1.8 g, 92%) as a solid. LCMS (Method I): Rt = 1.82 min, m/z = 336.1 $[M+H]^+$, 87.58%. This material was used without further purification.

Intermediate 33. *tert*-Butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

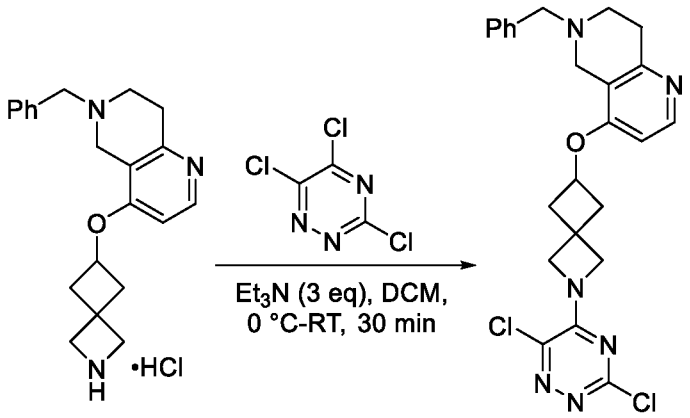


The reaction was performed following the same procedure in two batches, 359 mg and 25.6 mg batches.

To a stirred solution of 3,5,6-trichloro-1,2,4-triazine (359 mg, 1.947 mmol) in DCM (15 mL), TEA (0.547 mL, 3.89 mmol) was added at 0 °C. To this reaction mixture, *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (700 mg, 1.947 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (5% MeOH in DCM). The reaction mixtures from both batches were combined. Water (25 mL) was added and the mixture was extracted with DCM

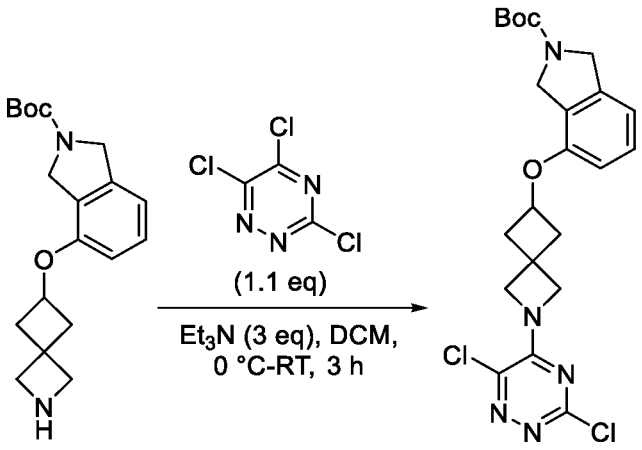
(3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 0-3% MeOH in DCM) to obtain *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (780 mg, 73.67% combined yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, J = 5.5 Hz, 1H), 6.75 (d, J = 5.8 Hz, 1H), 5.28 - 5.07 (m, 1H), 4.87 - 4.73 (m, 3H), 4.28 - 4.18 (m, 2H), 4.17 - 3.92 (m, 2H), 2.89 - 2.75 (m, 4H), 2.40 - 2.26 (m, 2H), 1.43 (br s, 9H), 1.33 (br d, J = 6.3 Hz, 3H); LCMS (Method H): Rt = 1.71 min, m/z = 507.2 $[M+H]^+$; 92.33%.

Intermediate 34. 6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine



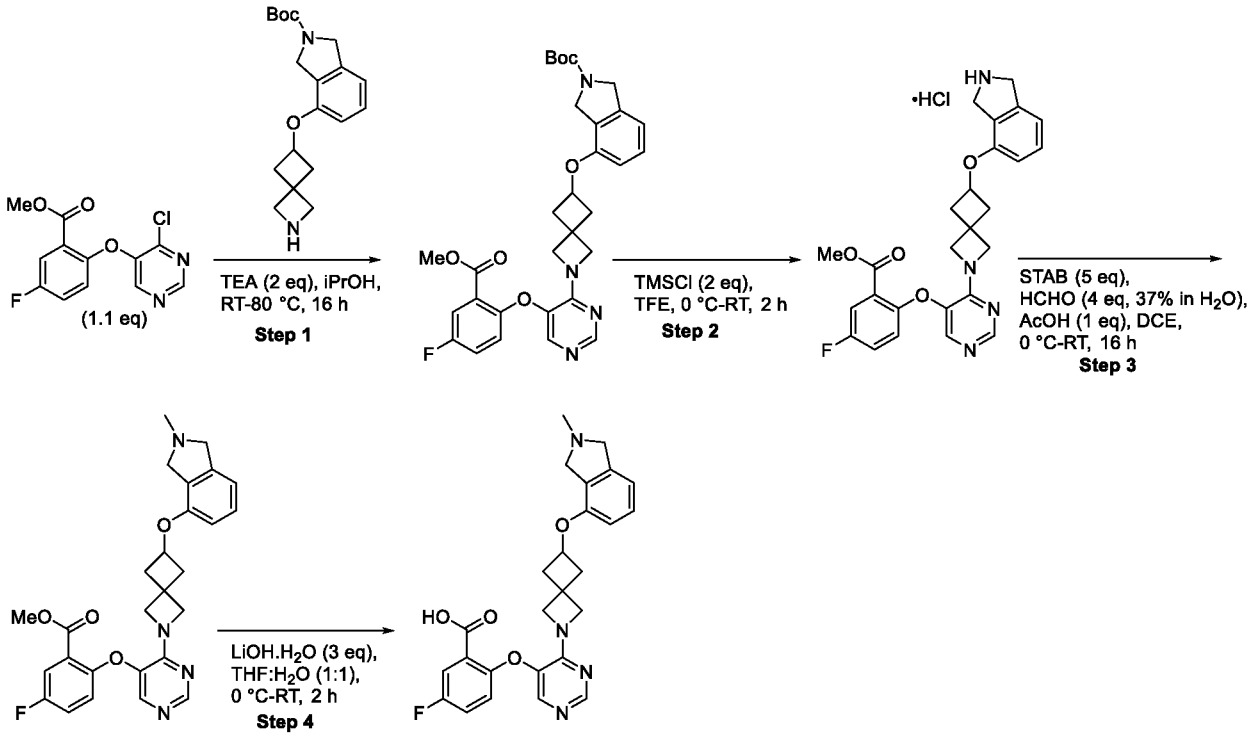
To a stirred solution of 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (49 g, 132 mmol) in DCM (490 mL), Et_3N (55.6 mL, 395 mmol) was added at 0 °C under a nitrogen atmosphere. To this reaction mixture, 3,5,6-trichloro-1,2,4-triazine (24.30 g, 132 mmol) was added, and the reaction was stirred at RT for 30 min. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with cold water (100 mL) and extracted with DCM (3 x 150 mL). The combined organic layer was washed with brine solution (200 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was triturated with 50% EtOAc in hexane (3 x 50 mL), and the organic layer was decanted. The resulting solid was dried under vacuum to obtain 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine (54 g, 85 % yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 5.6 Hz, 1H), 7.40 - 7.25 (m, 5H), 6.68 (d, J = 5.6 Hz, 1H), 4.81 - 4.67 (m, 3H), 4.25 - 4.12 (m, 2H), 3.71 (br s, 2H), 3.47 (br s, 2H), 2.85 - 2.77 (m, 4H), 2.72 (br s, 2H), 2.32 - 2.23 (m, 2H); LCMS (Method G): Rt = 2.08 min, m/z = 483.2 $[M+H]^+$; 99.84%.

Intermediate 35. *tert*-Butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate

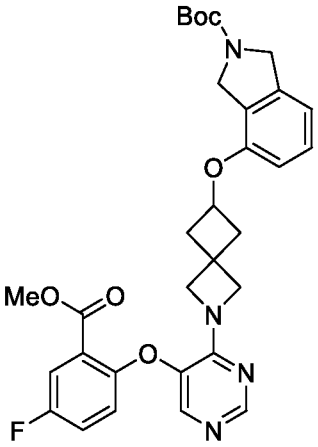


In a 100 mL two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.5 g, 4.54 mmol) was dissolved in DCM (20 mL), and Et_3N (2.268 mL, 16.27 mmol) was added at 0 °C. To this reaction mixture, 3,5,6-trichloro-1,2,4-triazine (0.921 g, 4.99 mmol) was added, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with water (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 50% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.1 g, 44.5% yield) as a solid. ^1H NMR (400 MHz, DMSO-d_6): δ 7.29 - 7.20 (m, 1H), 6.95 - 6.87 (m, 1H), 6.74 (d, J = 8.1 Hz, 1H), 4.81 (s, 1H), 4.77 - 4.68 (m, 2H), 4.57 (d, J = 10.5 Hz, 2H), 4.47 (d, J = 9.6 Hz, 2H), 4.25 (s, 1H), 4.18 (s, 1H), 2.83 - 2.79 (m, 2H), 2.37 - 2.29 (m, 2H), 1.46 (s, 9H); LCMS (Method H): Rt 2.45 min, m/z = 478.3 $[M+H]^+$, 87.89%

Intermediate 36. 5-Fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid



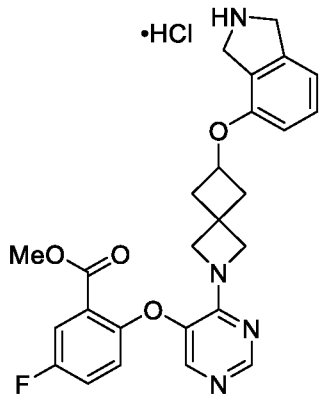
Step 1. tert-Butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



In a dried, 100 mL two neck round bottom flask, methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (1.411 g, 4.99 mmol) was added in 2-propanol (15 mL) under nitrogen atmosphere. To this solution, Et_3N (1.265 mL, 9.08 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.5 g, 4.54 mmol) were added at RT. The reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure, diluted with ice-cold water (30 mL), and extracted with EtOAc (2 x 100 mL). The

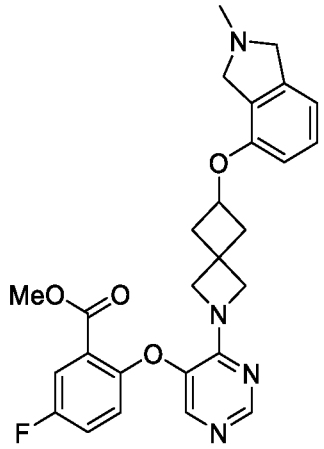
combined organic layer was washed with brine solution, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 80-90% EtOAc in hexane) to afford *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.6 g, 57.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.69 - 7.64 (m, 2H), 7.52 - 7.44 (m, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.16 - 7.03 (m, 1H), 6.89 (dd, J = 5.2, 7.3 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 4.71 (quin, J = 6.7 Hz, 1H), 4.56 (br d, J = 10.7 Hz, 2H), 4.44 (br d, J = 11.7 Hz, 2H), 4.27 (br s, 2H), 4.18 (s, 2H), 3.81 (s, 3H), 2.81 - 2.75 m, 2H), 2.31 - 2.20 (m, 2H), 1.46 (s, 9H); LCMS (Method B): Rt = 2.58 min, m/z = 577.2 $[M+H]^+$ 93.57%.

Step 2. Methyl 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate hydrochloride



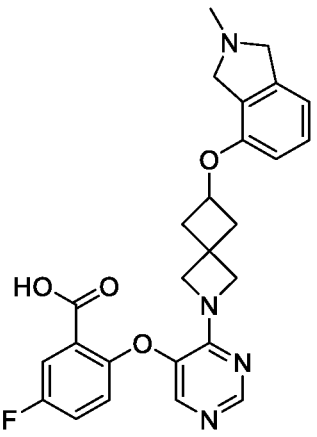
To a stirred solution of *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.6 g, 2.77 mmol) in 2,2,2-trifluoroethanol (5 mL), TMSCl (0.603 g, 5.55 mmol) was added at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (100% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to obtain crude methyl 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate hydrochloride (1.3 g, 84% yield). LCMS (Method B): Rt = 1.56 min, m/z = 477.4 $[M+H]^+$, 92.16%. This material was used without further purification.

Step 3. Methyl 5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate



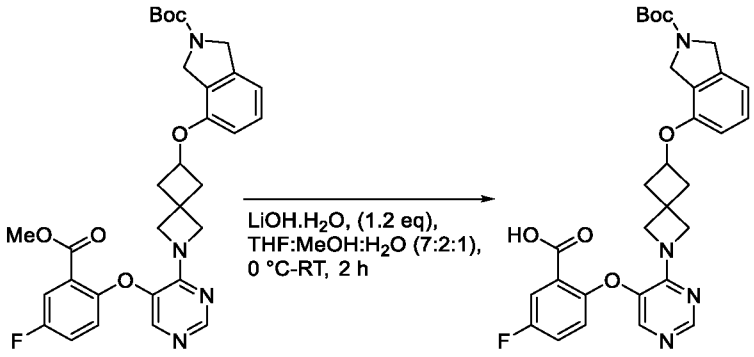
In a 50 mL round bottom flask under a nitrogen atmosphere, methyl 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate hydrochloride (1.3 g, 2.53 mmol) was added in DCE (10 mL). To this solution, formaldehyde (0.823 g, 10.14 mmol, 37% in H_2O) and acetic acid (0.152 g, 2.53 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (2.69 g, 12.67 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted with 10-20% MeOH in DCM) to obtain methyl 5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (0.99 g, 70.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 7.69 - 7.65 (m, 2H), 7.49 (ddd, J = 3.3, 7.9, 9.1 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.10 (dd, J = 4.5, 9.1 Hz, 1H), 6.88 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 4.74 - 4.65 (m, 1H), 4.29 - 4.25 (m, 2H), 4.18 (s, 2H), 4.17 - 4.05 (m, 4H), 3.82 (s, 3H), 2.81 - 2.74 (m, 2H), 2.70 (s, 3H), 2.28 - 2.20 (m, 2H); LCMS (Method B): Rt = 1.60 min, m/z = 491.2 $[M+H]^+$, 88.96%.

Step 4. 5-Fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid



In a pressure vial, methyl 5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (890 mg, 1.814 mmol) was added in THF (5 mL) and water (5 mL). To this solution, lithium hydroxide monohydrate (228 mg, 5.44 mmol) was added at 0 °C. The reaction was stirred at RT for 2 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. Water (10 mL) was added to this residue and the mixture was extracted with EtOAc (2 x 50 mL). The aqueous layer was acidified with 1N HCl and extracted with 10% MeOH in DCM (2 x 50 mL). The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain crude 5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid (500 mg, 56.3% yield) as a solid. LCMS (Method B): Rt = 1.49 min, m/z = 477.2 $[M+H]^+$; 97.48%. This material was used without further purification.

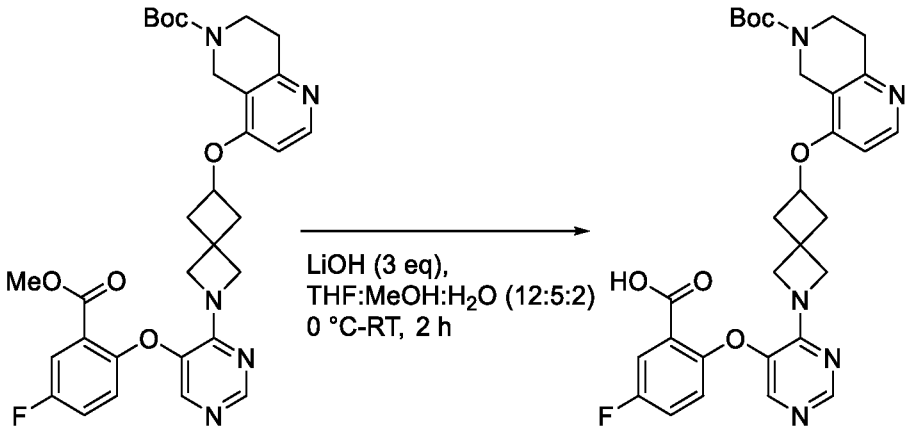
Intermediate 37. 2-((4-(6-((2-(*tert*-Butoxycarbonyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid



In a 100 mL round bottom flask, *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (600 mg, 1.041 mmol) was added in THF (7 mL) and MeOH (2 mL). To this solution, $LiOH.H_2O$ (52.4 mg, 1.249 mmol) dissolved in water (1 mL) was added at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH

in DCM). After completion, the reaction was concentrated under reduced pressure. The aqueous layer was diluted with water (25 mL), neutralized with 1.5 N HCl (2 mL), and extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 2-((4-(6-((2-(*tert*-butoxycarbonyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid (600 mg, 96% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.38 (br s, 1H), 8.25 (s, 1H), 7.64 - 7.52 (m, 2H), 7.46 - 7.34 (m, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.09 (dd, J = 4.6, 9.0 Hz, 1H), 6.89 (dd, J = 5.1, 7.3 Hz, 1H), 6.73 (br d, J = 8.3 Hz, 1H), 4.71 (quin, J = 6.2 Hz, 1H), 4.56 (br d, J = 11.0 Hz, 2H), 4.45 (br d, J = 10.5 Hz, 2H), 4.30 (br s, 2H), 4.20 (br s, 2H), 2.82 - 2.71 (m, 2H), 2.30 - 2.22 (m, 2H), 1.45 (s, 9 H); LCMS (Method D): Rt = 1.55 min, m/z = 563.1 $[M+H]^+$; 94.07%. This material was used without further purification.

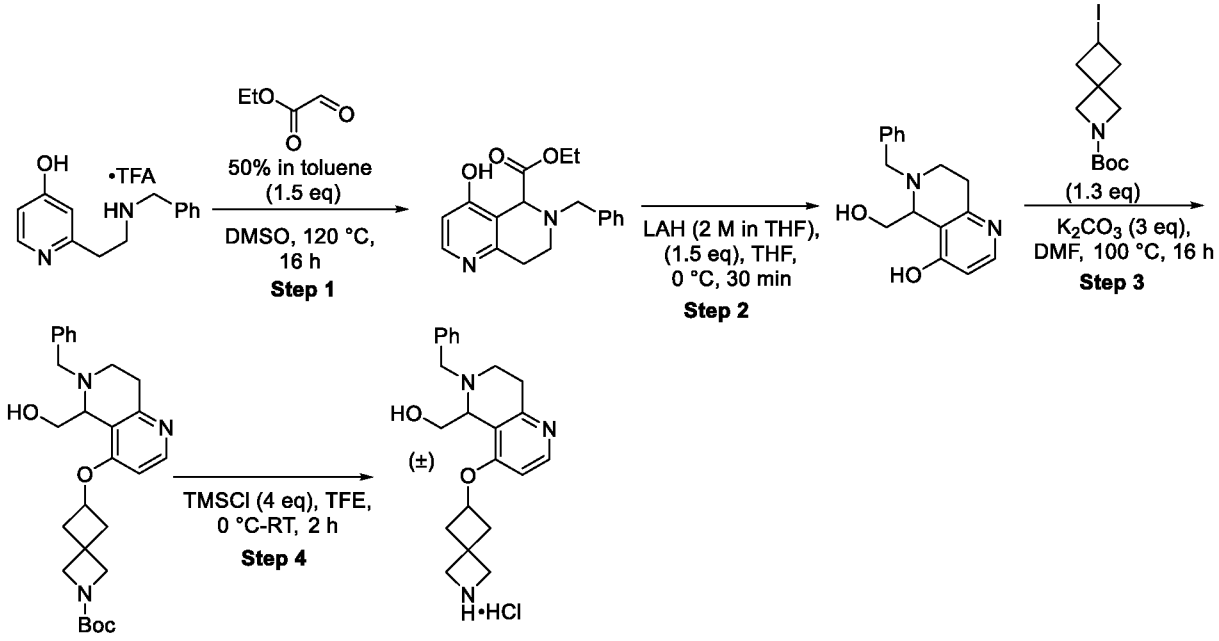
Intermediate 38. 2-((4-(6-((6-(*tert*-Butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid



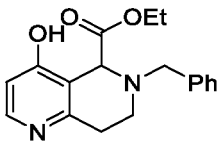
To a stirred solution of *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.75 g, 1.268 mmol) in THF:MeOH:H_2O (12:5:2, 19 mL), LiOH.H_2O (0.091 g, 3.80 mmol) was added at 0 °C. The reaction was stirred for 2 h at RT. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, ice-cold water (20 mL) was added to the reaction and the mixture was extracted with EtOAc (2 x 15 mL). The aqueous layer was acidified (to pH ~6) with 0.5N HCl and extracted with 10% MeOH in DCM (2 x 20 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford crude 2-((4-(6-((6-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-

yl)oxy)-5-fluorobenzoic acid (0.570 g, 74.7% yield) as a solid. LCMS (Method B): Rt = 21.71 min, m/z = 578.2 $[M+H]^+$,96.64%. This material was used without further purification.

Intermediate 39. (±)-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanol hydrochloride

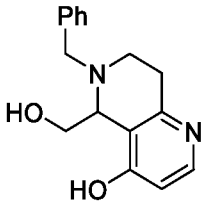


Step 1. (±)-Ethyl 6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carboxylate



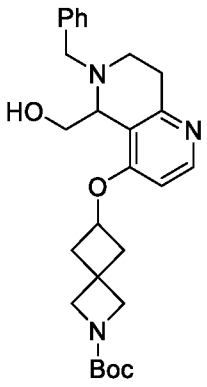
In a dried, 250 mL two neck round bottom flask under a nitrogen atmosphere, 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetate (5 g, 14.61 mmol) was added in DMSO (100 mL). To this solution, ethyl 2-oxoacetate (4.47 g, 21.91 mmol, 50% in toluene) was added at RT, and the reaction was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC (20% MeOH in DCM). After completion, the reaction was diluted with ice-cold water (100 mL) and extracted with 10% MeOH in DCM (2 x 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain (±)-ethyl 6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carboxylate (3.05 g, 42.6% yield). LCMS (Method B): Rt = 1.33 min, m/z = 313.3 $[M+H]^+$, 99.40%.

Step 2. (±)-6-Benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



In a dried, 250 mL two neck round bottom flask under a nitrogen atmosphere, (±)-ethyl 6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carboxylate (3 g, 9.60 mmol) was added in THF (40 mL). To this solution, LAH (7.20 mL, 14.41 mmol, 2 M in THF) was added at 0 °C, and the reaction was stirred at the same temperature for 30 min. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to -15 °C and quenched with aqueous sodium sulfate solution (10 mL). The reaction was extracted with 20% MeOH in DCM (200 mL) and filtered. The filtrate was concentrated under reduced pressure to afford crude (±)-6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (2.5 g, 92% yield) as a solid. LCMS (Method G): Rt = 1.22 min, m/z = 271.3 $[M+H]^+$, 96.32%. This material was used without further purification.

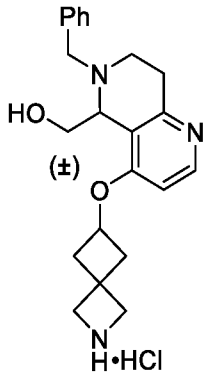
Step 3. (±)-tert-Butyl 6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.5 g, 5.55 mmol) in DMF (20 mL), powered K_2CO_3 (2.301 g, 16.65 mmol) was added at RT. The reaction was stirred for 10 min at RT. To this solution, *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (2.331 g, 7.21 mmol) was added at RT, and the reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, water (20 mL) was added to the reaction and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with ice-cold water (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using

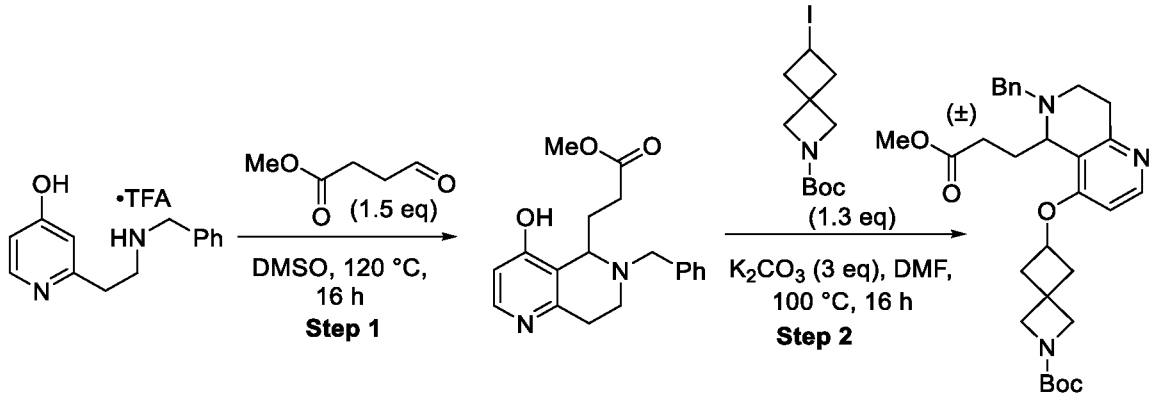
EtOAc in hexane (product eluted at 80% EtOAc in hexane) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1.5 g, 50.5% yield) as a solid. LCMS (Method B): Rt = 1.34 min, m/z = 466.4 $[M+H]^+$, 87.75%.

Step 4. (±)-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanol hydrochloride

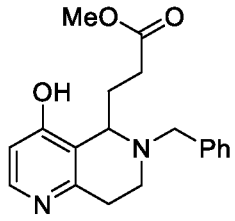


In a dried, 50 mL round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.7 g, 1.503 mmol) was added in TFE (2 mL). TMSCl (0.763 mL, 6.01 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude (±)-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanol hydrochloride (0.5 g, 55.5% yield) as a solid. LCMS (Method G): Rt = 1.40 min, m/z = 366.4 $[M+H]^+$, 67.12%.

Intermediate 40. (±)-*tert*-Butyl 6-((6-benzyl-5-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



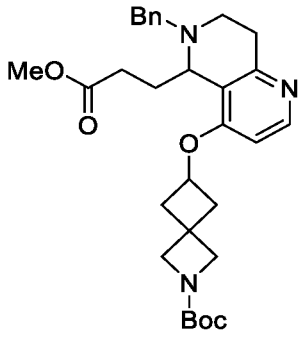
Step 1. (±)-Methyl 3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoate



To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetate (5 g, 14.61 mmol) in DMSO (125 mL), methyl 4-oxobutanoate (2.54 g, 21.91 mmol) was added at RT. The reaction was stirred at 120 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, water (50 mL) was added to the reaction and the mixture was extracted with 10% MeOH in DCM (3 x 50 mL). The product was observed in the aqueous layer. Therefore, the aqueous layer was basified with $NaHCO_3$ solution (20 mL) and re-extracted with 10% MeOH in DCM (2 x 50 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain (±)-methyl 3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoate (1.77 g, 33.4 % yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.22 (br d, J = 3.8 Hz, 1H), 7.54 - 7.46 (m, 1H), 7.36 - 7.23 (m, 5H), 5.95 (d, J = 7.1 Hz, 1H), 3.68 - 3.49 (m, 5H), 3.44 (br dd, J = 3.2, 9.9 Hz, 1H), 3.13 - 3.03 (m, 1H), 2.77 - 2.65 (m, 2H), 2.46 - 2.37 (m, 1H), 2.28 - 2.17 (m, 2H), 2.04 - 1.94 (m, 1H), 1.74 - 1.62 (m, 1H); ^{19}F NMR (377 MHz, DMSO-d_6): δ -73.41 (s, 3F); LCMS (Method G): Rt = 1.56 min, m/z = 327.3 $[M+H]^+$; 89.83%.

Note: An unknown amount of TFA was present.

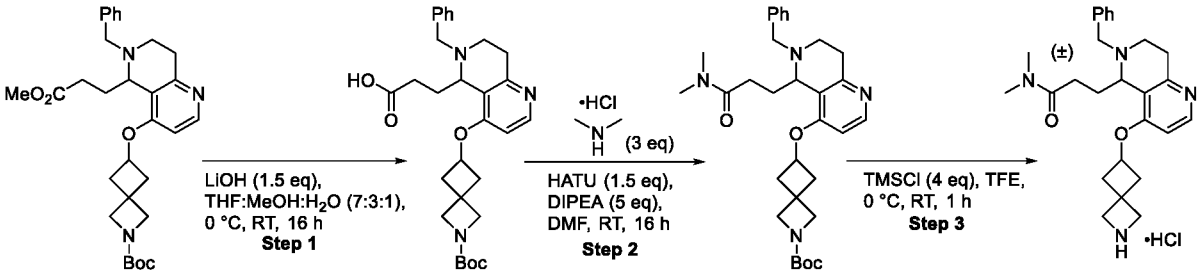
Step 2. (±)-tert-Butyl 6-((6-benzyl-5-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



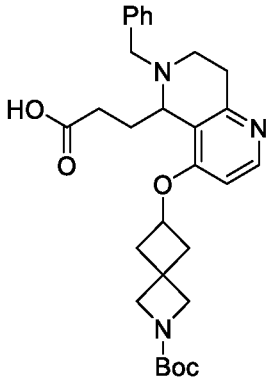
To a stirred solution of (±)-methyl 3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoate (3.8 g, 11.64 mmol) in DMF (20 mL), powered K_2CO_3 (4.83 g,

34.9 mmol) was added. The reaction was stirred at RT for 10 min. To this reaction mixture, *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (4.89 g, 15.13 mmol) was added, and the reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with ice-cold water (50 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 80% EtOAc in hexane) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (4.5 g, 60.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, J = 5.6 Hz, 1H), 7.37 - 7.22 (m, 5H), 6.68 (d, J = 5.8 Hz, 1H), 4.72 (quin, J = 6.4 Hz, 1H), 3.97 - 3.77 (m, 5H), 3.65 (s, 2H), 3.57 - 3.54 (m, 3H), 3.53 - 3.49 (m, 1H), 3.21 - 3.10 (m, 1H), 2.97 - 2.91 (m, 1H), 2.81 - 2.75 (m, 1H), 2.72 - 2.66 (m, 1H), 2.47 - 2.31 (m, 3H), 2.24 - 2.09 (m, 2H), 2.01 - 1.89 (m, 1H), 1.85 - 1.73 (m, 1H), 1.37 (s, 9H); LCMS (Method B): Rt = 1.67 min, m/z = 522.3 $[M+H]^+$, 82.35%.

Intermediate 41. (±)-3-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylpropanamide hydrochloride



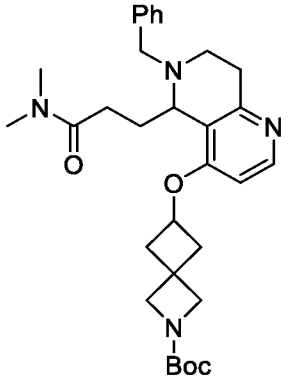
Step 1. (±)-3-(6-Benzyl-4-((2-(tert-butoxycarbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoic acid



In a 50 mL round bottom flask, (±)-tert-butyl 6-((6-benzyl-5-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (450 mg,

0.863 mmol) was added in THF (3 mL), MeOH (1.3 mL) and water (0.4 mL). To this solution, lithium hydroxide monohydrate (54.3 mg, 1.294 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. Water (5 mL) was added to the residue. The mixture was acidified with 1.5 N HCl (pH ~3-5) and extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude (±)-3-(6-benzyl-4-((2-(*tert*-butoxycarbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoic acid (420 mg, 95% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (br s, 1H), 8.38 (br d, J = 5.9 Hz, 1H), 7.37 - 7.31 (m, 4H), 7.31 - 7.24 (m, 1H), 6.89 (br d, J = 5.1 Hz, 1H), 4.88 - 4.78 (m, 1H), 3.90 (br s, 2H), 3.83 (br s, 2H), 3.78 - 3.69 (m, 1H), 3.64 - 3.54 (m, 1H), 3.25 - 3.16 (m, 1H), 3.05 - 2.94 (m, 1H), 2.84 - 2.69 (m, 3H), 2.66 - 2.55 (m, 2H), 2.40 - 2.30 (m, 2H), 2.27 - 2.15 (m, 2H), 1.97 - 1.75 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 1.60 min, m/z = 508.5 $[M+H]^+$; 99.30%. This material was used without further purification.

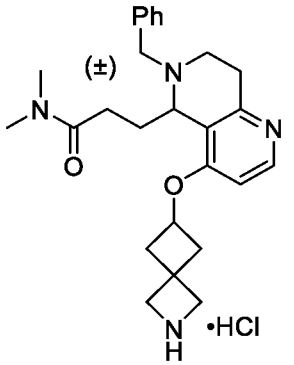
Step 2. (±)-tert-Butyl 6-((6-benzyl-5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-3-(6-benzyl-4-((2-(*tert*-butoxycarbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoic acid (420 mg, 0.827 mmol) in DMF (5 mL) under nitrogen atmosphere, dimethylamine hydrochloride (202 mg, 2.482 mmol), HATU (472 mg, 1.241 mmol), and DIPEA (0.723 mL, 4.14 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was quenched with ice water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted

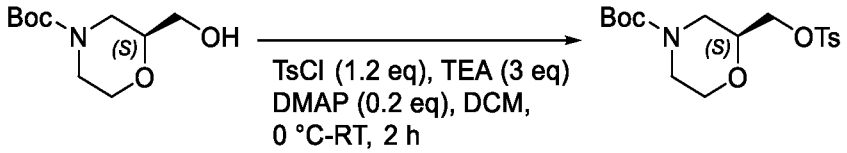
at 5% MeOH in DCM) to afford (±)-*tert*-butyl 6-((6-benzyl-5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (330 mg, 74.2% yield) as a solid. LCMS (Method G): Rt = 2.05 min, m/z = 535.6 $[M+H]^+$; 99.43%.

Step 3. (±)-3-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylpropanamide hydrochloride



In a dried, 50 mL round bottom flask, (±)-*tert*-butyl 6-((6-benzyl-5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (330 mg, 0.617 mmol) was added in 2,2,2-trifluoroethanol (4 mL). TMSCl (0.316 mL, 2.469 mmol) was added to this solution at 0 °C, and the reaction was stirred to RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropanamide hydrochloride (290 mg, 86% yield) as a solid. LCMS (Method G): Rt = 2.33 min, m/z = 435.3 $[M+H]^+$; 86.51%. This material was used without further purification.

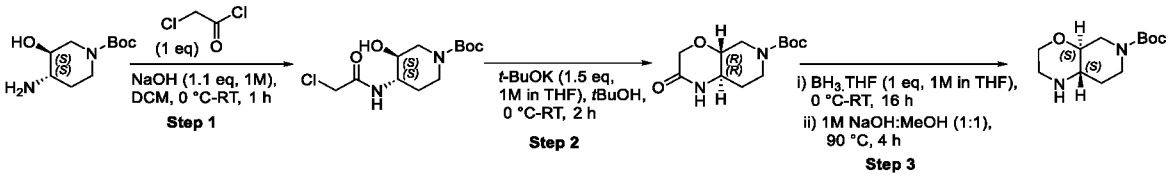
Intermediate 42. *tert*-Butyl (S)-2-((tosyloxy)methyl)morpholine-4-carboxylate



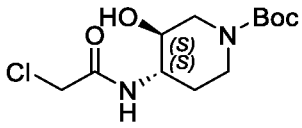
To a stirred solution of *tert*-butyl (*S*)-2-(hydroxymethyl)morpholine-4-carboxylate (500 mg, 2.301 mmol) in DCM (5 mL), TEA (0.962 mL, 6.90 mmol) was added at RT. DMAP (56.2 mg, 0.460 mmol) and pTsCl (526 mg, 2.76 mmol) were added to this reaction mixture. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to 0 °C quenched with ice-cold water (25 mL), and extracted with DCM (3 x 35 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced

pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 10-12% EtOAc in hexane) to obtain *tert*-butyl (*S*)-2-((tosyloxy)methyl)morpholine-4-carboxylate (700 mg, 81% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 - 7.78 (m, 2H), 7.52 - 7.47 (m, 2H), 4.11 - 4.06 (m, 1H), 4.04 - 3.98 (m, 1H), 3.79 - 3.62 (m, 3H), 3.56 - 3.49 (m, 1H), 3.38 - 3.35 (m, 1H), 2.89 - 2.73 (m, 1H), 2.65 - 2.57 (m, 1H), 2.43 (s, 3H), 1.39 (s, 9H); LCMS (Method D): Rt = 2.19 min, m/z = 272.1 $[M-100]^+$, 98.95%.

Intermediate 43. *tert*-Butyl (4a*S*,8a*S*)-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate

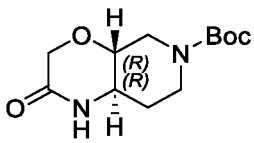


Step 1. tert-Butyl (3S,4S)-4-(2-chloroacetamido)-3-hydroxypiperidine-1-carboxylate



To a stirred solution of *tert*-butyl (3*S*,4*S*)-4-amino-3-hydroxypiperidine-1-carboxylate (5 g, 23.12 mmol) in DCM (20 mL), 1M NaOH (25.4 mL, 25.4 mmol) was added at 0 °C. The reaction was stirred at the same temperature for 2 min, and then, 2-chloroacetyl chloride (1.841 mL, 23.12 mmol) dissolved in DCM (5 mL) was added at 0 °C. The reaction was stirred at 0 °C for 5 min and then stirred at RT for 1 h. The reaction was monitored by TLC (100% EtOAc). The reaction was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl (3*S*,4*S*)-4-(2-chloroacetamido)-3-hydroxypiperidine-1-carboxylate (6 g, 20.39 mmol, 88% yield) as a liquid. LCMS-ELSD (Method B): Rt = 2.10 min, m/z = 193.3 $[M-Boc+H]^+$; 99.65%. This material was used without further purification.

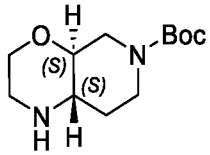
Step 2. tert-Butyl (4aR,8aR)-2-oxooctahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate



In a 250 mL two neck round bottom flask under nitrogen atmosphere, *tert*-butyl (3*S*,4*S*)-4-(2-chloroacetamido)-3-hydroxypiperidine-1-carboxylate (6 g, 20.49 mmol) was added in *t*-

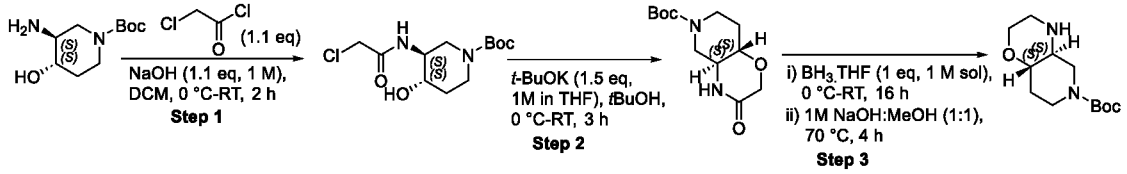
BuOH (20 mL). To this solution, potassium *tert*-butoxide (30.7 mL, 30.7 mmol, 1M in THF) was added at 0 °C. The reaction was stirred at RT for 2 h. The reaction was monitored by TLC (100% EtOAc). The reaction was quenched with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 60% EtOAc in hexane). The pure fractions were concentrated under reduced pressure to obtain *tert*-butyl (4a*S*,8a*S*)-2-oxooctahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (3 g, 56% yield) as a solid. LCMS-ELSD (Method G): Rt = 1.42 min, m/z = 257.1 $[M+H]^+$; 98.44%.

Step 3. tert-Butyl (4aS,8aS)-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate

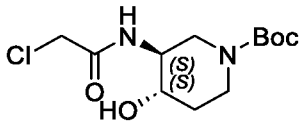


To a stirred solution of *tert*-butyl (4a*S*,8a*S*)-2-oxooctahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (3 g, 11.70 mmol) in THF (15 mL), BH_3.THF (11.70 mL, 11.70 mmol, 1M in THF) was added at 0 °C. The reaction was stirred at RT for 16 h. 1M NaOH: MeOH (1:1, 90 mL) was added to this reaction at 0 °C. The reaction was stirred at 90 °C for 4 h. The reaction was monitored by TLC (100% EtOAc). The reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (4a*S*,8a*S*)-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (2.8 g, 83% yield) as a liquid. LCMS-ELSD (Method B): Rt = 1.66 min, m/z = 243.4 $[M+H]^+$; 84.38%. This material was used without further purification.

Intermediate 44. *tert*-Butyl (4a*S*,8a*S*)-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate

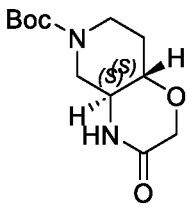


Step 1. tert-Butyl (3S,4S)-3-(2-chloroacetamido)-4-hydroxypiperidine-1-carboxylate



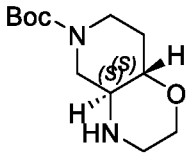
To a stirred solution of *tert*-butyl (3*S*,4*S*)-3-amino-4-hydroxypiperidine-1-carboxylate (10 g, 46.2 mmol) in DCM 20 mL), 1M NaOH (50.9 mL, 50.9 mmol) was added at 0 °C. To this reaction mixture, 2-chloroacetyl chloride (4.05 mL, 50.9 mmol) in DCM (10 mL) was added slowly, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (3*S*,4*S*)-3-(2-chloroacetamido)-4-hydroxypiperidine-1-carboxylate (13.0 g, 95% yield) as a semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (br s, 1H), 4.08 (s, 2H), 3.96 - 3.89 (m, 1H), 3.85 - 3.74 (m, 2H), 3.74 - 3.65 (m, 1H), 3.32 - 3.18 (m, 2H), 1.98 - 1.88 (m, 1H), 1.67 - 1.56 (m, 1H), 1.50 - 1.47 (s, 9H); one proton was merged with solvent peaks; LCMS (Method D): Rt = 1.37 min, m/z = 291.2 $[M-H]^+$, 87.53%. This material was used without further purification.

Step 2. tert-Butyl (4aS,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate



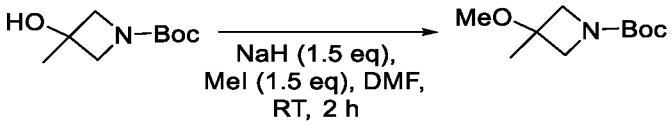
In a 500 mL two neck round bottom flask under argon atmosphere, *tert*-butyl (3*S*,4*S*)-3-(2-chloroacetamido)-4-hydroxypiperidine-1-carboxylate (13 g, 44.4 mmol) was dissolved in *t*-BuOH (130 mL). To this solution, potassium *tert*-butoxide (66.6 mL, 66.6 mmol; 1M in THF) was added at °C, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was cooled to 0 °C, quenched with water (80 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 100% EtOAc) to obtain *tert*-butyl (4a*S*,8a*S*)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (7.0 g, 61.1% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (br s, 1H), 4.18 - 3.99 (m, 4H), 3.40 - 3.34 (m, 2H), 3.03 - 2.95 (m, 1H), 2.90 - 2.69 (m, 1H),1.89 - 1.81 (m, 1H), 1.42 (m, 9H), 1.38 - 1.32 (m, 1H); LCMS (Method C): Rt = 1.64 min, m/z = 255.1 $[M-H]^-$, 97.83%. Chiral SFC (Method I): Rt = 1.46 min, 100%

Step 3. tert-Butyl (4aS,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate



To a stirred solution of *tert*-butyl (4a*S*,8a*S*)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (7.0 g, 27.3 mmol) in THF (70 mL), borane tetrahydrofuran complex (54.6 mL, 54.6 mmol; 1M in THF) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred at RT for 16 h. The progress reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to 0 °C and quenched with methanol (70 mL) and 1M NaOH (70 mL). The reaction was stirred at 70 °C for 4 h. The reaction was cooled to RT and concentrated under reduced pressure. Water (50 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using methanol in DCM (product was eluted at 5% MeOH in DCM) to obtain *tert*-butyl (4a*S*,8a*S*)-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (3.0 g, 44.9% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.04 - 3.82 (m, 2H), 3.75 - 3.69 (m, 1H), 3.52 - 3.44 (m, 1H), 3.09 - 3.00 (m, 1H), 2.83 - 2.68 (m, 3H), 2.47 - 2.30 (m, 1H), 2.25 - 2.16 (m, 1H), 1.71 - 1.64 (m, 1H), 1.42 - 1.37 (s, 9H), 1.35 - 1.22 (m, 1H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.46 min, m/z = 243.3 $[M+H]^+$, 99.76%. Chiral SFC (Method AU): Rt = 1.83 min, 80.16%.

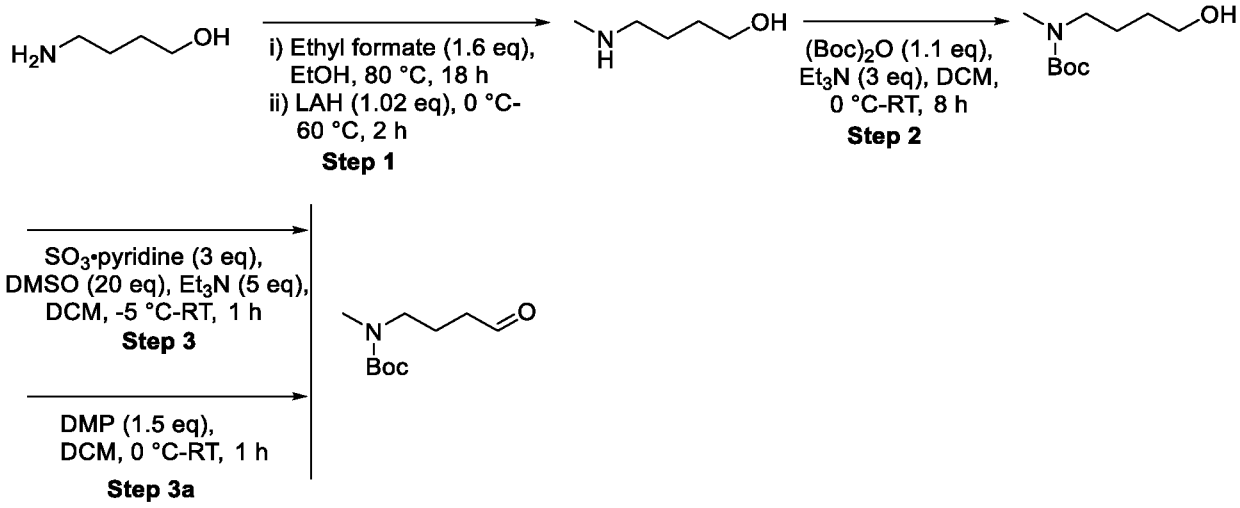
Intermediate 45. *tert*-Butyl 3-methoxy-3-methylazetidine-1-carboxylate



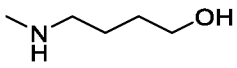
In a 25 mL two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-hydroxy-3-methylazetidine-1-carboxylate (500 mg, 2.67 mmol) was added in DMF (5 mL). To this solution, NaH (160 mg, 4.01 mmol) and MeI (0.249 mL, 4.01 mmol) were added at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 3-methoxy-3-methylazetidine-1-carboxylate (350

mg, 65.1% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (d, *J* = 8.9 Hz, 2H), 3.68 (d, *J* = 9.5 Hz, 2H), 3.25 (s, 3H), 1.47 (s, 3H), 1.46 (s, 9H).

Intermediate 46. *tert*-Butyl methyl(4-oxobutyl)carbamate

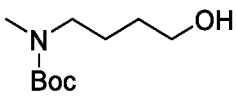


Step 1. 4-(Methylamino)butan-1-ol



In a dried, 50 mL round bottom flask under a nitrogen atmosphere, 4-aminobutan-1-ol (2 g, 22.44 mmol) was added in ethanol (25 mL). To this solution, ethyl formate (2.66 g, 35.9 mmol) was added, and the reaction was stirred at 80 °C for 18 h. After completion, the reaction was concentrated under reduced pressure. The residue was re-concentrated from toluene (3 x 7 mL) under reduced pressure to afford crude *N*-(4-hydroxybutyl)formamide. This compound was dissolved in THF (13 mL), and LAH (23 mL, 23.00 mmol, 1M in THF) was added at 0 °C. The reaction was stirred at 60 °C for 2 h. The progress of the reaction was monitored by NMR. After completion, the reaction was cooled to 0 °C and quenched with water (4 mL) and 15% aq. NaOH (1 mL). The resulting reaction mixture was dried over sodium sulfate and filtered through a Celite® pad, and the pad was washed with THF (10 mL). The filtrate was concentrated under reduced pressure to afford crude 4-(methylamino)butan-1-ol (2.3 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 - 3.54 (m, 2H), 2.69 - 2.60 (m, 2H), 2.45 (s, 3H), 1.75 - 1.57 (m, 4H), two protons merged with solvent peaks.

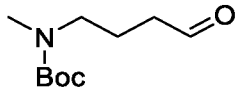
Step 2. tert-Butyl (4-hydroxybutyl)(methyl)carbamate



In a dried, 50 mL round bottom flask under a nitrogen atmosphere, 4-(methylamino)butan-1-ol (1.5 g, 14.54 mmol) was added in DCM (15 mL). To this solution, $(Boc)_2O$ (3.71 mL, 15.99

mmol) and Et_3N (6.08 mL, 43.6 mmol) were added at 0 °C. The reaction was stirred RT for 8 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and the residue was washed with *n*-hexane (3 x 10 mL). The hexane layer was concentrated under reduced pressure to afford crude *tert*-butyl (4-hydroxybutyl)(methyl)carbamate (2.2 g, 74.4% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.38 (t, J = 5.2 Hz, 1H), 3.39 (q, J = 6.2 Hz, 2H), 3.14 (t, J = 7.1 Hz, 2H), 2.75 (s, 3H), 1.54 - 1.32 (m, 13H); LCMS (Method B): Rt = 1.90 min, m/z = 104.2 [M+H-100]$^+$, 95.62%. This material was used without further purification.

Step 3. tert-Butyl methyl(4-oxobutyl)carbamate

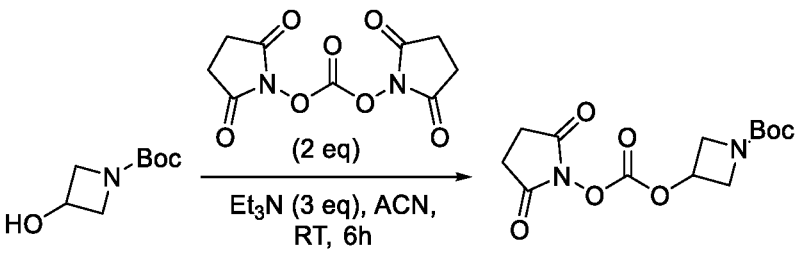


To a stirred solution of *tert*-butyl (4-hydroxybutyl)(methyl)carbamate (400 mg, 1.968 mmol) in DCM (8 mL), DMSO (2.80 mL, 39.4 mmol) and Et_3N (1.383 mL, 9.84 mmol) were added at RT. Sulfur trioxide pyridine complex (940 mg, 5.90 mmol) was added portion-wise to this reaction mixture at -5 °C. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was basified (to pH ~8) with 10% NaOH solution (2 mL) and saturated $NaHCO_3$ solution (5 mL), and extracted with DCM (3 x 15 mL). The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl methyl(4-oxobutyl)carbamate (390 mg, 98% yield) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 3.27 (t, J = 6.9 Hz, 2H), 2.86 (s, 3H), 2.51 - 2.43 (m, 2H), 1.91 - 1.85 (m, 2H), 1.47 (s, 9H). This material was used without further purification.

Step 3a. tert-Butyl methyl(4-oxobutyl)carbamate

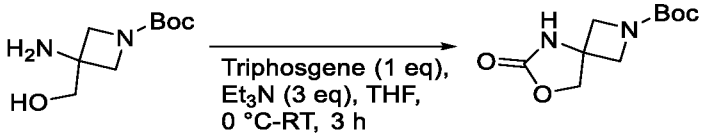
In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl (4-hydroxybutyl)(methyl)carbamate (1 g, 4.92 mmol) was added in DCM (10 mL). To this solution, Dess-Martin periodinane (3.13 g, 7.38 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). The reaction was quenched with sodium bicarbonate solution (30 mL) and extracted with DCM (2 x 50 mL). The organic layer was concentrated under reduced pressure. The crude product was diluted with saturated sodium thiosulfate (30 mL) and re-extracted with (50% EtOAc in hexane). The organic layer was concentrated under reduced pressure to obtain crude *tert*-butyl methyl(4-oxobutyl)carbamate (800 mg, 81% yield). This material was used without further purification.

Intermediate 47. *tert*-Butyl 3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)azetidine-1-carboxylate



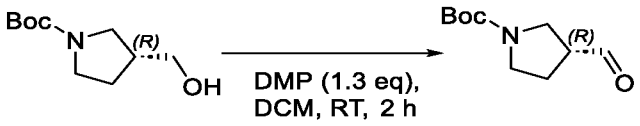
To a stirred solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (1.0 g, 5.77 mmol) in ACN (20 mL), Et_3N (2.414 mL, 17.32 mmol) and disuccinimidyl carbonate (2.96 g, 11.55 mmol) were added at RT. The reaction was stirred at the same temperature for 6 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure. Water (30 mL) was added to the crude and the mixture was extracted with EtOAc (3 x 45 mL). The combined organic layer was washed with water (100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)azetidine-1-carboxylate (1.6 g, 88% yield) as a solid. ^{1}H NMR (400 MHz, C*D*Cl_3): δ 5.19 - 5.07 (m, 1H), 4.13 - 4.07 (m, 2H), 4.02 - 3.95 (m, 2H), 1.46 (s, 9H). This material was used without further purification.

Intermediate 48. *tert*-Butyl 6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate



In a 50 mL two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-amino-3-(hydroxymethyl)azetidine-1-carboxylate (500 mg, 2.472 mmol) was added in THF (4 mL). To this solution, Et_3N (1.042 mL, 7.42 mmol) and triphosgene (734 mg, 2.472 mmol) were added at 0 °C, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 4% MeOH in DCM) to obtain *tert*-butyl 6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate (350 mg, 61.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (s, 1H), 4.47 (s, 2H), 4.06 - 3.86 (m, 4H), 1.38 (s, 9H); LCMS (Method B): Rt = 1.44 min, m/z = 129.2 $[M+H]^+$, 98.94%.

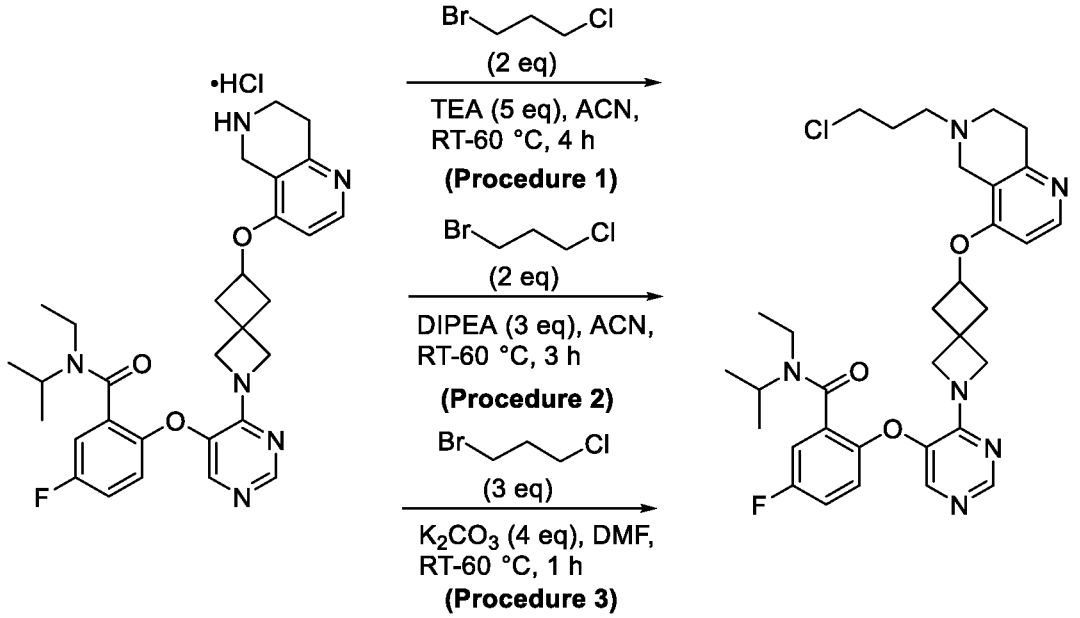
Intermediate 49. *tert*-Butyl (*R*)-3-formylpyrrolidine-1-carboxylate



In a dried, 50 mL two-neck round bottom flask under nitrogen atmosphere, *tert*-butyl (*R*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.25 g, 1.242 mmol) was added in DCM (5 mL). To this solution, Dess-Martin periodinane (0.685 g, 1.615 mmol) was added in one portion at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was diluted with DCM (50 mL) and washed with saturated $NaHCO_3$ solution (2 x 30 mL). The organic layer was washed with saturated sodium thiosulfate solution (3 x 50 mL). The combined organic layer was washed with water (2 x 20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (*R*)-3-formylpyrrolidine-1-carboxylate (0.200 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, J = 1.5 Hz, 1H), 3.80 - 3.31 (m, 4H), 3.04 (br s, 1H), 2.26 - 2.06 (m, 2H), 1.48 (s, 9H). This material was used without further purification.

Note: ^{1}HNMR showed impurity peaks along with product peaks.

Intermediate 50. 2-((4-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



Procedure 1.

In a 30 mL pressure vial, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

hydrochloride (300 mg, 0.514 mmol) was added in ACN (5 mL). To this solution, TEA (0.359 mL, 2.57 mmol) and 1-bromo-3-chloropropane (0.102 mL, 1.029 mmol) were added at RT. The reaction was heated to 60 °C and stirred for 4 h. The reaction progress was monitored by TLC (20% MeOH in DCM). When complete, the reaction was concentrated under reduced pressure. Water (10 mL) was added, and the mixture was extracted with DCM (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted in 8% MeOH in DCM) to obtain 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (100 mg, 31.2% yield) as a solid. LCMS (Method B): Rt = 1.68 min, m/z = 623.3 $[M+H]^+$; 91.86%.

Procedure 2.

The reaction was performed following the same procedure in two batches, 1.5 g and 3 g batches.

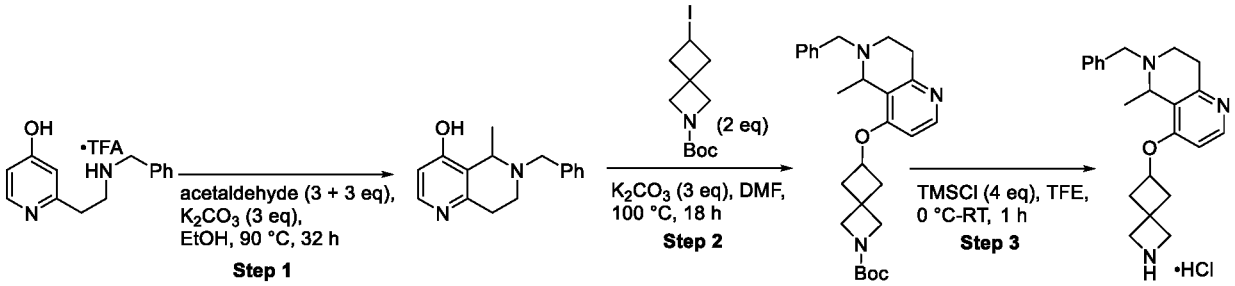
In a pressure vial, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (1.5 g, 2.57 mmol) was added in ACN (15 mL). To this solution, DIPEA (1.348 mL, 7.72 mmol) and 1-bromo-3-chloropropane (0.810 g, 5.14 mmol) were added at RT. The reaction was heated to 60 °C and stirred for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, both reactions were mixed and concentrated under reduced pressure. Water (50 mL) was added, and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (1.8 g, 31.2% combined yield) as a solid. LCMS (Method B): Rt = 1.68 min, m/z = 623.3 $[M+H]^+$; 97.92%.

Procedure 3

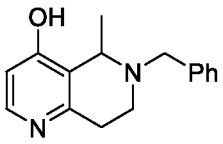
To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (3 g, 5.14 mmol) in DMF (20 mL), powdered K_2CO_3 (2.84 g, 20.58 mmol) and 1-bromo-3-chloropropane (2.430 g, 15.43 mmol) was added at RT. The reaction was stirred at 60 °C for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM).

After completion, the reaction was diluted with ice-cold water (50 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (1.8 g, 39.7% yield). LCMS (Method G): Rt = 1.99 min, m/z = 623.6 $[M+H]^+$; 70.74%. This material was used without further purification.

Intermediate 51. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



Step 1. 6-(±)-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



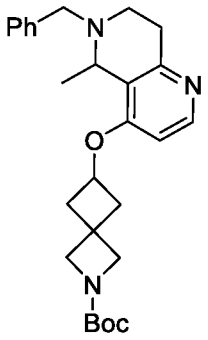
The reaction was performed following the same procedure in four batches (4 x 10 g).

To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (10 g, 29.2 mmol) in EtOH (100 mL), potassium carbonate (12.11 g, 88 mmol) and acetaldehyde (4.95 mL, 88 mmol) were added at RT. The reaction was stirred at 90 °C for 16 h under a nitrogen atmosphere. The starting material was not consumed by TLC (10% MeOH in DCM). To this reaction mixture, another lot of acetaldehyde (4.95 mL, 88 mmol) was added at RT. The reaction was stirred at 90 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction mixtures from four batches were combined and filtered through a Celite® pad, and the pad was washed with MeOH (2 x 200 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel

flash column chromatography using MeOH in DCM (product eluted at 20% MeOH in DCM) to afford 6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (18.5 g, 62.23% combined yield) as a solid. LCMS (Method G): Rt = 1.30 min, m/z = 255.2 $[M+H]^+$, 90.57%.

Note: Traces of TFA remained with the product.

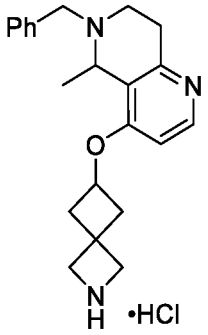
Step 2. (±)-tert-Butyl 6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



The reaction was performed following the same procedure in two batches.

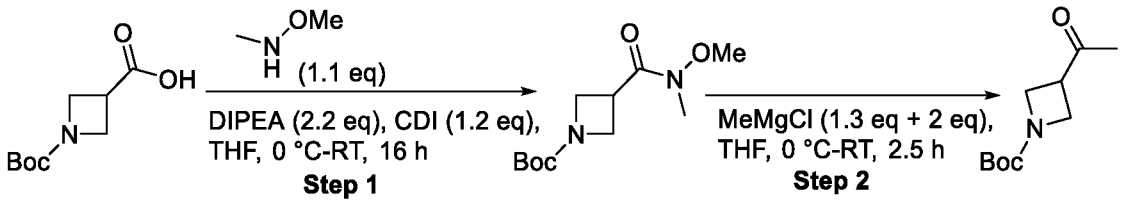
This compound was synthesized following the procedure described for the synthesis of Intermediate 32, step 1, starting with 2 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used. The reaction mixtures from both batches were combined and diluted with ice cold water, and the mixture was extracted with EtOAc. The aqueous layer was re-extracted with 10% MeOH in DCM. The combined organic layer was washed with cold water, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a sticky solid.
Combined yield: 55.64%; LCMS (Method B): Rt = 1.48 min, m/z = 450.2 $[M+H]^+$, 92.41%.

Step 3. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride

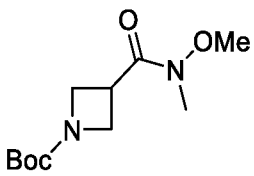


This compound was synthesized following the procedure described for the synthesis of Intermediate 32, step 2, starting with (±)-*tert*-butyl 6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. After completion, the reaction was concentrated under reduced pressure. The crude product was triturated with EtOAc, the supernatant was decanted, and the residue was dried under vacuum to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride as a solid. This material was used without further purification. Yield: 81%; LCMS (Method G): Rt = 1.52 min, m/z = 350.2 $[M+H]^+$, 77.81%.

Intermediate 52. *tert*-Butyl 3-acetylazetidine-1-carboxylate



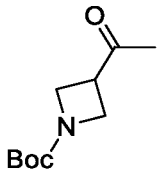
Step 1. tert-Butyl 3-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate



In a 100 mL two neck round bottom flask under a nitrogen atmosphere, 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (1 g, 4.97 mmol) was added in THF (20 mL). To

this solution, DIPEA (1.910 mL, 10.93 mmol) and *N*,*N*'-carbonyldiimidazole (0.967 g, 5.96 mmol) were added at 0 °C. The reaction was stirred at RT for 30 min. To this reaction mixture, *N*,O-dimethylhydroxylamine (0.334 g, 5.47 mmol) was added at 0 °C and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (80% EtOAc in hexane). The reaction was quenched with saturated ammonium chloride solution (30mL) and the mixture was extracted by EtOAc (3 x 30 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 40-50% EtOAc in hexane) to obtain *tert*-butyl 3-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate (900 mg, 73.9% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.03 - 3.84 (m, 4H), 3.76 - 3.67 (m, 1H), 3.63 (s, 3H), 3.11 (s, 3H), 1.38 (s, 9H).

Step 2. tert-Butyl 3-acetylazetidine-1-carboxylate

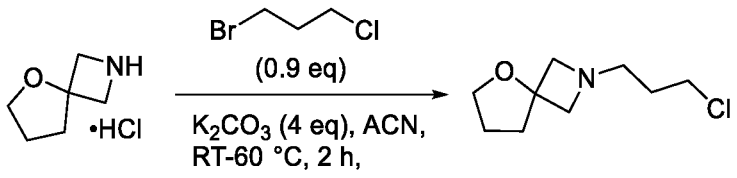


The reaction was performed following the same procedure in two batches (100 mg and 750 mg).

To a stirred solution of *tert*-butyl 3-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate (750 mg, 3.07 mmol) in THF (14 mL), methylmagnesium chloride (1.330 mL, 3.99 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred at RT for 2 h, then another lot of methylmagnesium chloride (2.047 mL, 6.14 mmol) was added at 0 °C. The reaction was stirred for 30 min at the same temperature. The reaction progress was monitored by TLC (80% EtOAc in hexane). After completion, the reaction mixtures from both batches were combined and quenched with cold water (10 mL). To this mixture, 10% citric acid solution (15 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 3-acetylazetidine-1-carboxylate (650 mg, 86.14% combined yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.99 - 3.82

(m, 4H), 3.57 - 3.48 (m, 1H), 2.12 (s, 3H), 1.37 (s, 9H); LCMS (Method B): Rt = 1.59 min, m/z = 100.3 $[M\text{-}Boc+H]^+$, 91.97%. This material was used without further purification.

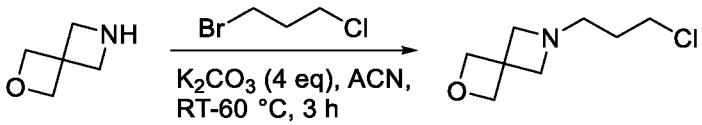
Intermediate 53. 2-(3-Chloropropyl)-5-oxa-2-azaspiro[3.4]octane



The reaction was performed following the same procedure in four batches (4 x 500 mg).

To a stirred solution of 5-oxa-2-azaspiro[3.4]octane hydrochloride (500 mg, 3.34 mmol) in ACN (10 mL), K_2CO_3 (1847 mg, 13.37 mmol) and 1-bromo-3-chloropropane (474 mg, 3.01 mmol) were added at RT under a nitrogen atmosphere. The reaction was stirred at 60 °C for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction mixture from four batches were combined and diluted with water (30 mL), and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (2 g, 78.86% combined yield) as a liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 - 3.76 (m, 2H), 3.59 (t, J = 6.6 Hz, 2H), 3.42 - 3.36 (m, 2H), 3.11 - 3.03 (m, 2H), 2.61 (t, J = 7.0 Hz, 2H), 2.15 - 2.09 (m, 2H), 1.94 - 1.79 (m, 4H). This material was used without further purification.

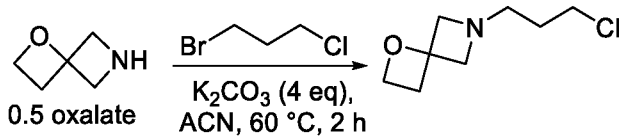
Intermediate 54. 6-(3-Chloropropyl)-2-oxa-6-azaspiro[3.3]heptane



This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 1 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of 2-oxa-6-azaspiro[3.3]heptane was used. After work-up, the filtrate was

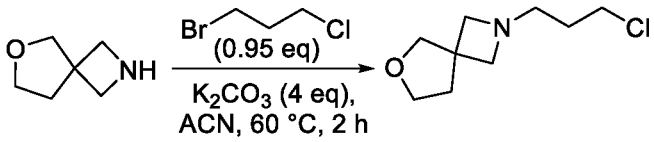
concentrated under reduced pressure to afford crude 6-(3-chloropropyl)-2-oxa-6-azaspiro[3.3]heptane as a liquid. This material was used without further purification. Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 4H), 3.57 (t, J = 6.5 Hz, 2H), 3.36 (s, 4H), 2.51 (t, J = 6.9 Hz, 2H), 1.80 (quin, J = 6.8 Hz, 2H).

Intermediate 55. 6-(3-Chloropropyl)-1-oxa-6-azaspiro[3.3]heptane



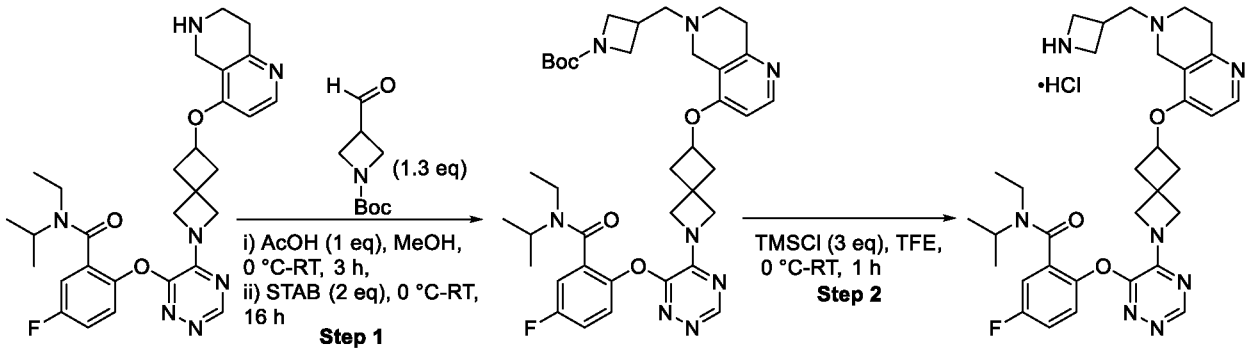
This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 1 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of 1-oxa-6-azaspiro[3.3]heptane hemi-oxalate was used. After work-up, the filtrate was concentrated under reduced pressure to afford crude 6-(3-chloropropyl)-1-oxa-6-azaspiro[3.3]heptane as a liquid. This material was used without further purification. Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53 (t, J = 7.6 Hz, 2H), 3.67 - 3.62 (m, 2H), 3.57 (t, J = 6.6 Hz, 2H), 3.16 - 3.11 (m, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.57 (t, J = 7.0 Hz, 2H), 1.86 - 1.79 (m, 2H).

Intermediate 56. 2-(3-Chloropropyl)-6-oxa-2-azaspiro[3.4]octane

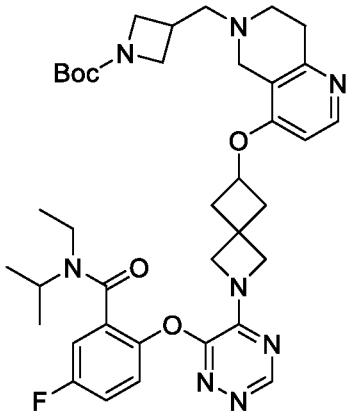


This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.95 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of 6-oxa-2-azaspiro[3.4]octane was used. After work-up, the filtrate was concentrated under reduced pressure to afford crude 2-(3-chloropropyl)-6-oxa-2-azaspiro[3.4]octane as a liquid. This material was used without further purification. Yield: 78%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 2H), 3.79 (t, J = 6.8 Hz, 2H), 3.58 (t, J = 6.4 Hz, 2H), 3.24 – 3.18 (m, 4H), 2.57 (t, J = 7.2 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 1.82 (quin, J = 7.2 Hz, 2H).

Intermediate 57. 2-((5-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride



Step 1. tert-Butyl 3-((4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate

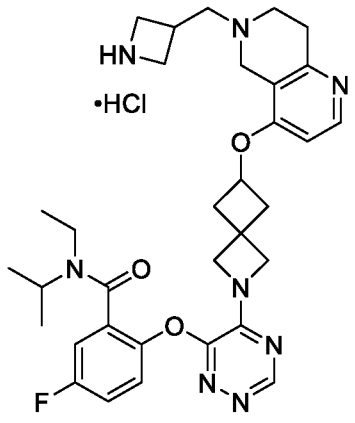


This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1.3 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, except that 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, 1 equivalent of AcOH, and 2 equivalents of STAB were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to obtain *tert*-

butyl 3-((4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate as a solid.

Yield: 31.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.49 - 7.31 (m, 3H), 6.68 (d, J = 5.8 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.66 - 4.50 (m, 2H), 4.32 - 4.06 (m, 2H), 3.99 - 3.83 (m, 2H), 3.67 - 3.47 (m, 3H), 3.43 (s, 2H), 3.14 - 2.99 (m, 1H), 2.89 - 2.75 (m, 5H), 2.74 - 2.68 (m, 4H), 2.37 - 2.24 (m, 2H), 1.37 (s, 9H), 1.17 - 0.68 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.03 min, m/z = 717.6 [M+H]$^+$, 89.85%.

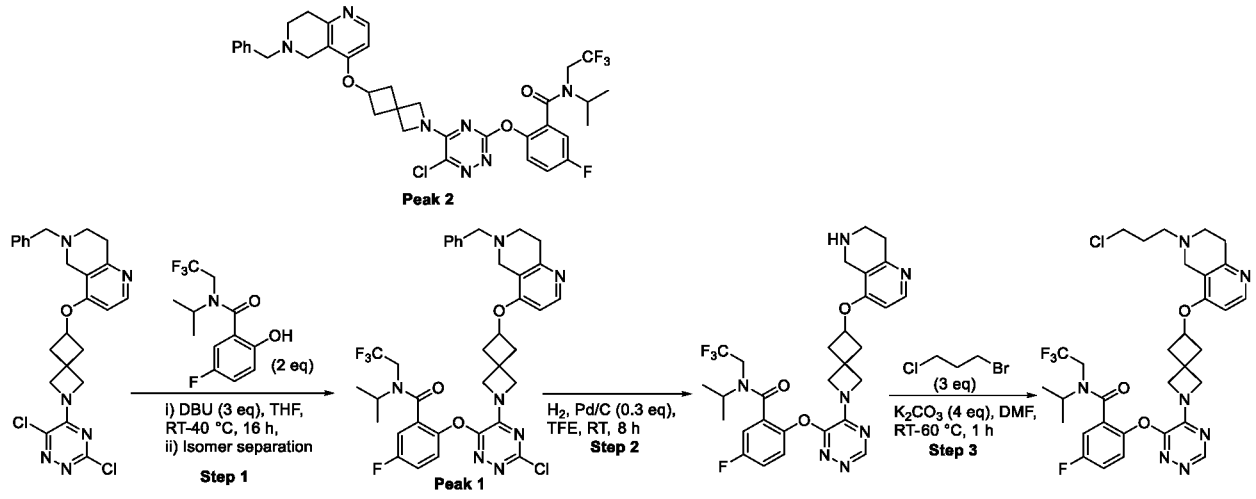
Step 2. 2-((5-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



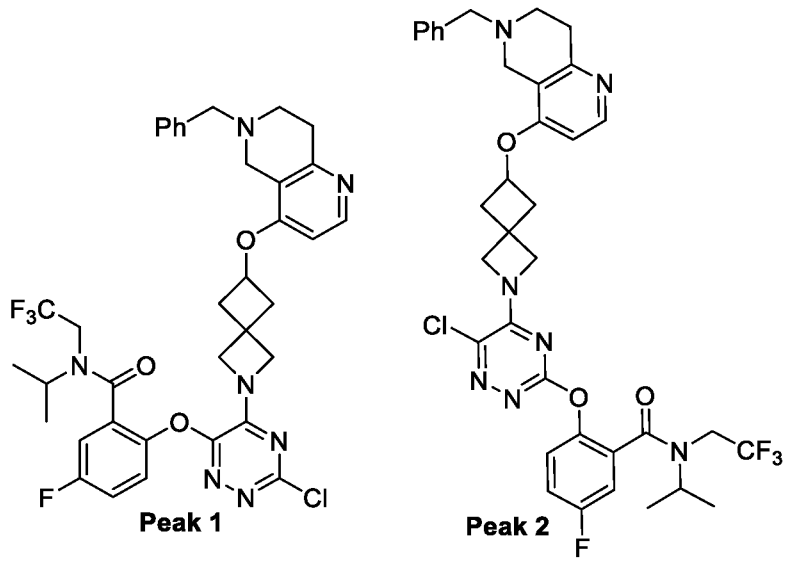
This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate. After completion, the residue was triturated with EtOAc, the supernatant was decanted, and the solid was dried under vacuum to obtain crude 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. This material was used without further purification.

Yield: 89% yield; LCMS (Method G): Rt = 1.62 min, m/z = 617.5 [M+H]$^+$, 86.59%.

Intermediate 58. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide



Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



In a 500 mL round bottom flask under a nitrogen atmosphere, 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine (9 g,

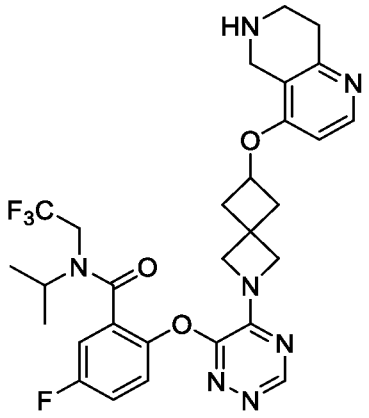
18.62 mmol) and 5-fluoro-2-hydroxy-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (10.40 g, 37.2 mmol) were added in THF (180 mL). DBU (8.42 mL, 55.9 mmol) was added to this reaction mixture at RT and the reaction was stirred at 40 °C for 18 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was diluted with water (200 mL) and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and the other regioisomer (11.6 g, 76% yield) as a solid. LCMS (Method G): Rt = 2.44 min, m/z = 726.3 $[M+H]^+$, 88.71%.

The mixture of regioisomers (7 g) was purified by achiral Prep SFC (Method F) to obtain both regioisomers.

Peak 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.
Yield: 36.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (t, J = 5.6 Hz, 1H), 7.53 - 7.40 (m, 3H), 7.38 - 7.23 (m, 5H), 6.67 (dd, J = 5.8, 8.3 Hz, 1H), 4.75 (quin, J = 6.6 Hz, 1H), 4.67 - 4.49 (m, 2H), 4.31 - 4.03 (m, 4H), 3.81 - 3.62 (m, 3H), 3.47 (s, 2H), 2.87 - 2.67 (m, 6H), 2.37 - 2.17 (m, 2H), 1.37 - 0.67 (m, 6H); LCMS (Method D): Rt = 2.31 min, m/z = 726.2 $[M+H]^+$; HPLC (Method A): Rt = 7.39 min, 97.28%.

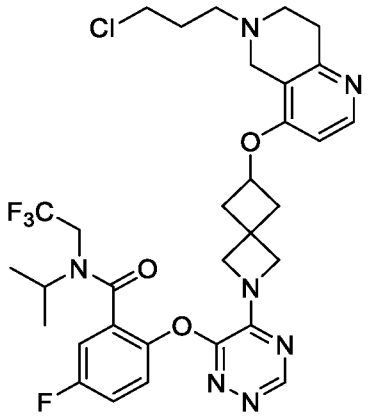
Peak 2. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.
Yield: 30.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (br d, J = 5.6 Hz, 1H), 7.42 - 7.24 (m, 8H), 6.67 (br d, J = 5.5 Hz, 1H), 4.80 - 4.57 (m, 3H), 4.31 - 3.95 (m, 4H), 3.93 - 3.79 (m, 1H), 3.69 (s, 2H), 3.46 (s, 2H), 2.85 - 2.66 (m, 6H), 2.33 - 2.19 (m, 2H), 1.27 - 0.99 (m, 6H); LCMS (Method G): Rt = 2.44 min, m/z = 726.3 $[M+H]^+$; HPLC (Method A): Rt = 7.51 min, 97.89%.

Step 2. 5-Fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



In a 100 mL round bottom flask, Pd/C (dry; 1.288 g, 1.210 mmol) was added at RT to a stirred solution of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (2.93 g, 4.03 mmol) in TFE (30 mL). The reaction was stirred at RT for 8 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 60 mL). The filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to obtain 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (1.65 g, 67.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.52 - 7.33 (m, 3H), 6.66 (br d, J = 4.8 Hz, 1H), 4.76 (quin, J = 6.7 Hz, 1H), 4.66 - 4.42 (m, 2H), 4.36 - 3.98 (m, 4H), 3.83 - 3.74 (m, 1H), 3.70 (br s, 2H), 2.95 (br t, J = 5.4 Hz, 2H), 2.88 - 2.75 (m, 2H), 2.68 (br t, J = 5.4 Hz, 2H), 2.38 - 2.23 (m, 2H), 1.28 - 0.68 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.68 min, m/z = 602.2 $[M+H]^+$, 99.85%.

Step 3. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide

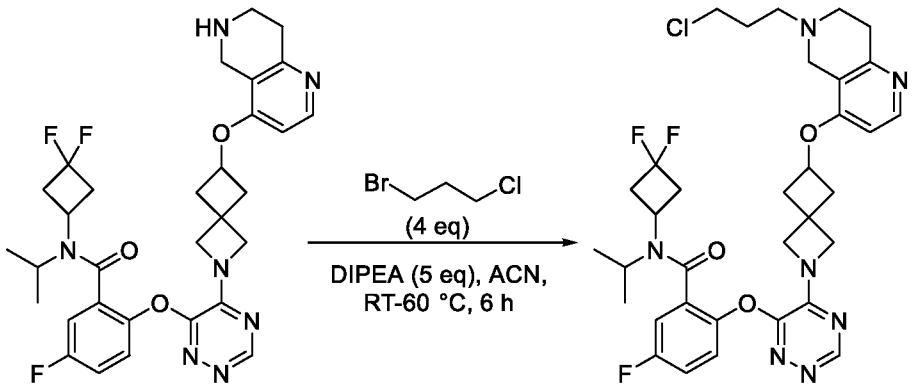


The reaction was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalents of 1-bromo-3-chloropropane, except that 1 equivalent of 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide was used. The reaction mixtures from both batches were combined and worked-up to afford crude 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid. This material was used without further purification.

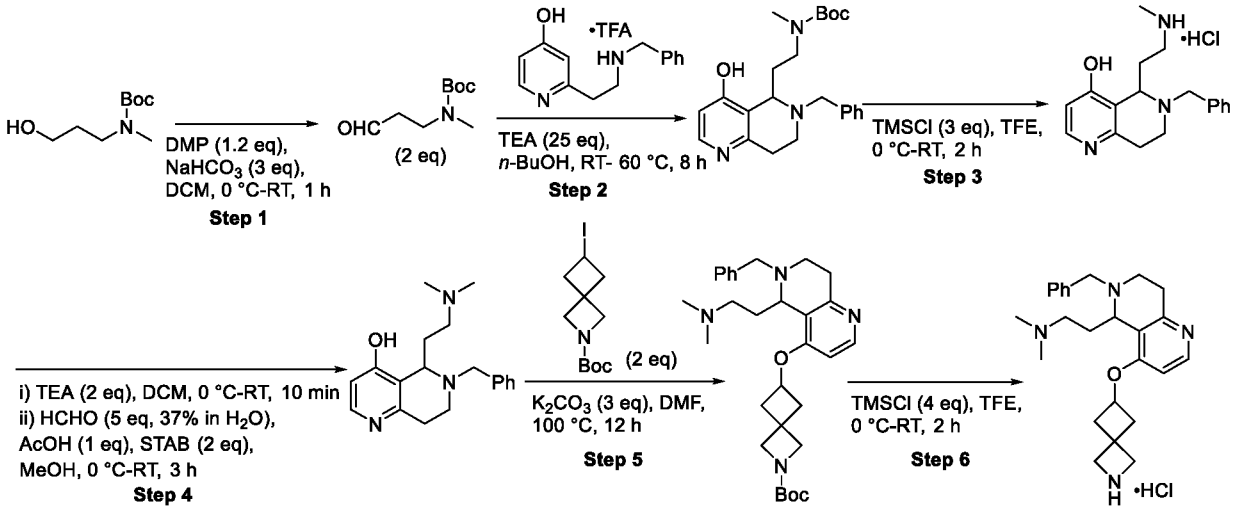
Combined yield: 84.22%; LCMS (Method F): Rt = 2.33 min, m/z = 678.5 $[M+H]^+$, 95.11%.

Intermediate 59. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide

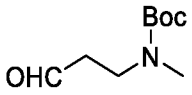


This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 2, starting with *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 4 equivalents of 1-bromo-3-chloropropane and 5 equivalents of DIPEA were used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (0.078 g, 54.7% yield) as a solid. LCMS (Method G): Rt = 1.97 min, m/z = 686.5 $[M+H]^+$, 79.57%.

Intermediate 60. 2-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylethan-1-amine hydrochloride

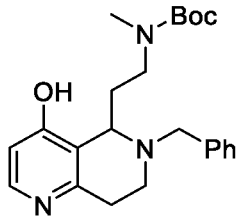


Step 1. tert-Butyl methyl(3-oxopropyl)carbamate



In a dried, 250 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl (3-hydroxypropyl)(methyl)carbamate (7.5 g, 39.6 mmol) was added in DCM (100 mL). To this solution, Dess-Martin periodinane (20.17 g, 47.6 mmol) and $NaHCO_3$ (9.99 g, 119 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad and the pad was washed with DCM (100 mL). The filtrate was washed with 10% $NaHCO_3$ solution (2 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. Hexane (100 mL) was added to this residue, and the mixture was stirred for 15 min then filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl methyl(3-oxopropyl)carbamate (6.80 g, 92% yield) as a liquid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 3.45 (t, J = 6.6 Hz, 2H), 2.82 - 2.72 (m, 3H), 2.62 (t, J = 5.9 Hz, 2H), 1.38 (s, 9H).

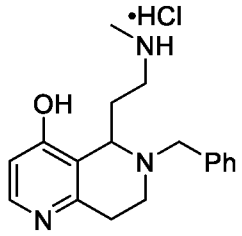
Step 2. (±)-tert-Butyl (2-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)(methyl)carbamate



To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (6.0 g, 18.39 mmol) in *n*-butanol (60 mL), *tert*-butyl methyl(3-oxopropyl)carbamate (6.89 g, 36.8 mmol) and Et_3N (64.6 mL, 460 mmol) were added at RT. The reaction was stirred at 60 °C for 8 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The residue was diluted with saturated $NaHCO_3$ solution (50 mL) and the mixture was extracted with EtOAc (3 x 50

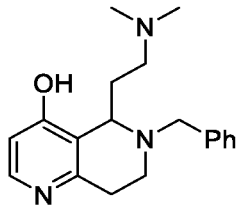
mL). The combined organic layer was washed with water (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 15-20% MeOH in DCM) to obtain (±)-*tert*-butyl (2-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)(methyl)carbamate (5.1 g, 69.2% yield) as a solid. LCMS (Method G): Rt = 1.77 min, m/z = 398.4 $[M+H]^+$, 98.23%.

Step 3. (±)-6-Benzyl-5-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with 1 equivalent of (±)-*tert*-butyl (2-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)(methyl)carbamate, to obtain crude (±)-6-benzyl-5-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride as a solid. This material was used without further purification.
Yield: 96%; LCMS (Method G): Rt = 1.24 min, m/z = 298.3 $[M+H]^+$, 96.82%.

Step 4. (±)-6-Benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol

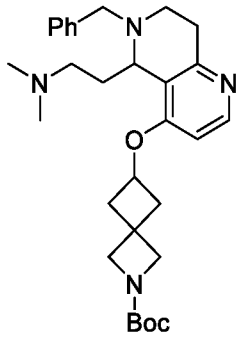


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with (±)-6-benzyl-5-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride, except that 5 equivalents of formaldehyde (37% in H_2O) and 2 equivalents of STAB were used. After completion, the reaction was concentrated under

reduced pressure. The residue was diluted with 10% MeOH in DCM and washed with saturated $NaHCO_3$. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain crude (±)-6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol. This material was used without further purification.

Yield: 67.5%; LCMS (Method G): Rt = 1.14 min, m/z = 312.3 $[M+H]^+$, 92.38%.

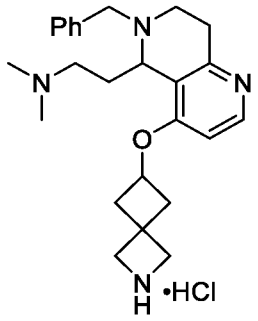
Step 5. (±)-tert-Butyl 6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 39, step 3, starting with 2 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used. After completion, the reaction was diluted with EtOAc and filtered through a Celite® pad, and the pad was washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*tert*-butyl 6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a solid.

Yield: 49.1%; LCMS (Method G): Rt = 2.20 min, m/z = 507.5 $[M+H]^+$, 98.86%.

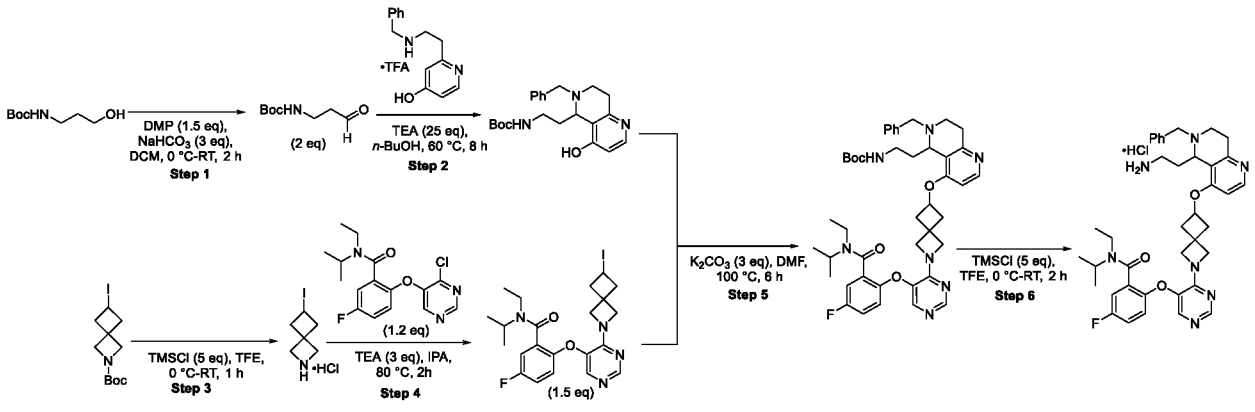
Step 6. (±)-2-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylethan-1-amine hydrochloride



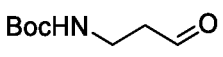
This compound was synthesized following the procedure described for the synthesis of Intermediate 39, step 4, starting with 1 equivalent of (±)-*tert*-butyl 6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. After completion, the reaction was concentrated under reduced pressure. The residue was triturated with EtOAc, and the supernatant was decanted. The solid was dried under reduced pressure to obtain crude (±)-2-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylethan-1-amine hydrochloride. This material was used without further purification.

Yield: 70.4%; LCMS (Method G): Rt = 1.33 min, m/z = 407.4 $[M+H]^+$, 64.81%.

Intermediate 61. (±)-2-((4-(6-((5-(2-Aminoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

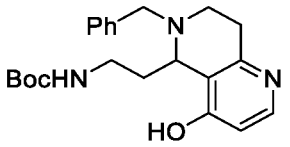


Step 1. tert-Butyl (3-oxopropyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 1, starting with 1 equivalent of *tert*-butyl (3-hydroxypropyl)carbamate, except that 1.5 equivalents of Dess-Martin periodinane was used, to obtain crude *tert*-butyl (3-oxopropyl)carbamate as a liquid. This material was used without further purification.
Yield: 64.1%.

Step 2. (±)-tert-Butyl (2-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 2, starting with 1 equivalent of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 2 equivalents of *tert*-butyl (3-oxopropyl)carbamate was used, to obtain (±)-*tert*-butyl (2-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)carbamate as a solid.
Yield: 35.8%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.26 (br s, 1H), 7.52 (br t, J = 5.7 Hz, 1H), 7.39 - 7.20 (m, 5H), 6.77 (br s, 1H), 5.96 (br d, J = 7.0 Hz, 1H), 3.74 - 3.61 (m, 1H), 3.60 - 3.48 (m, 2H), 3.19 - 3.03 (m, 2H), 3.01 - 2.84 (m, 1H), 2.83 - 2.63 (m, 2H), 2.36 - 2.18 (m, 1H), 1.77 - 1.65 (m, 1H), 1.63 - 1.50 (m, 1H), 1.37 (s, 9H); LCMS (Method G): Rt = 1.63 min, m/z = 384.2 $[M+H]^+$, 97.44%.

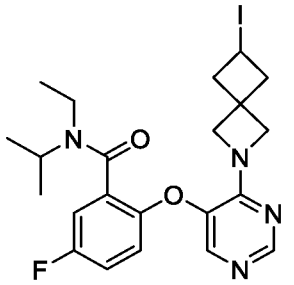
Step 3. 6-Iodo-2-azaspiro[3.3]heptane hydrochloride



In a 100 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (2.0 g, 6.19 mmol) was added in 2,2,2 trifluoroethanol (20 mL). To this solution, TMSCl (3.93 mL, 30.9 mmol) was added at 0 °C and the reaction

was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The residue was triturated with EtOAc (3 x 10 mL), and the supernatant was decanted. The residue was dried under reduced pressure to obtain crude 6-iodo-2-azaspiro[3.3]heptane hydrochloride (1.6 g, quantitative yield) as a solid. This material was used without further purification.[1]H NMR (400 MHz, DMSO-d_6): δ 9.05 (br s, 2H), 4.41 (quin, J = 8.0 Hz, 1H), 3.95 (s, 4H), 3.01 – 2.91 (m, 2H), 2.71 – 2.54 (m, 2H).

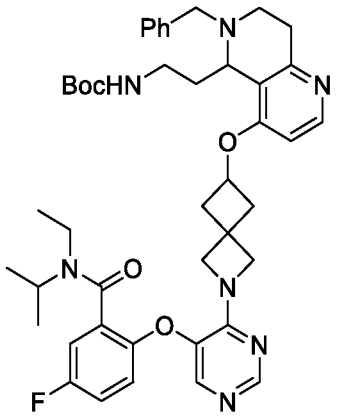
Step 4. N-Ethyl-5-fluoro-2-((4-(6-iodo-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1.2 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of 6-iodo-2-azaspiro[3.3]heptane hydrochloride was used. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain *N*-ethyl-5-fluoro-2-((4-(6-iodo-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 81%; [1]H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.25 (m, 1H), 7.73 – 7.65 (m, 1H), 7.34 – 7.21 (m, 2H), 7.08 – 6.98 (m, 1H), 4.51 – 4.36 (m, 1H), 4.27 – 4.11 (m, 4H), 3.74 (spt, J = 6.8 Hz, 1H), 3.46 – 3.35 (m, 1H), 3.29 – 3.08 (m, 1H), 3.01 – 2.89 (m, 2H), 2.72 – 2.62 (m, 2H), 1.25 – 0.97 (m, 9H); LCMS (Method G): Rt = 2.26 min, m/z = 525.3 $[M+H]^+$, 98.08%.

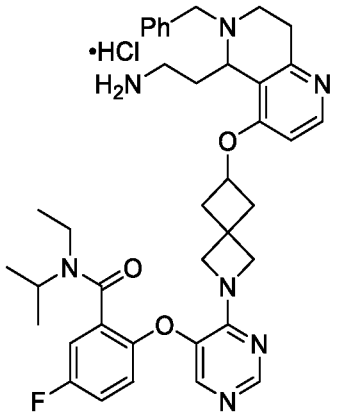
Step 5. (±)-tert-Butyl (2-(6-benzyl-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 39, step 3, except that 1 equivalent of (±)-*tert*-butyl (2-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)carbamate and 1.5 equivalents of *N*-ethyl-5-fluoro-2-((4-(6-iodo-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide were used. After completion, the reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine solution, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain (±)-*tert*-butyl (2-(6-benzyl-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)carbamate as a solid.

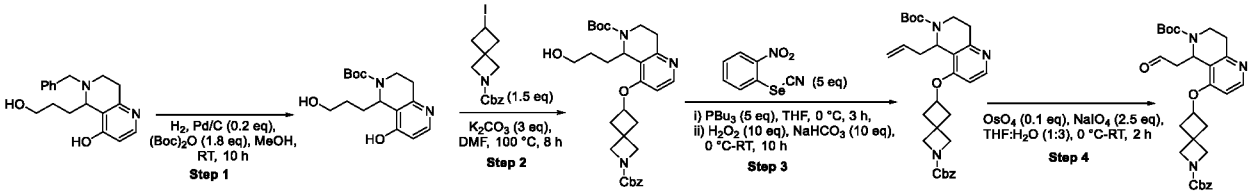
Yield: 53.4% yield; LCMS (Method G): Rt = 2.29 min, m/z = 780.3 $[M+H]^+$, 83.47%.

Step 6. (±)-2-((4-(6-((5-(2-Aminoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride

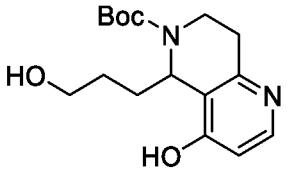


This compound was synthesized following the procedure described for the synthesis of Intermediate 39, step 4, starting with 1 equivalent of (±)-*tert*-butyl (2-(6-benzyl-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethyl)carbamate, except that 5 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure. The residue was triturated with EtOAc, and the supernatant layer was decanted. The solid was dried under reduced pressure to obtain crude (±)-2-((4-(6-((5-(2-aminoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (65 mg, 59.2% yield) as a solid. This material was used without further purification. LCMS (Method G): Rt = 1.82 min, m/z = 680.2 $[M+H]^+$, 83.67%.

Intermediate 62. (±)-*tert*-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-oxoethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

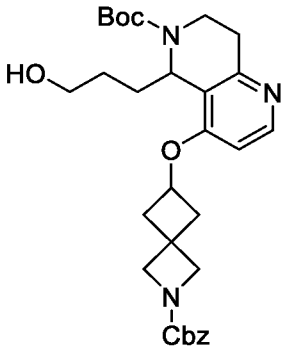


Step 1. (±)-tert-Butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a dried, 500 mL round bottom flask under a nitrogen atmosphere, (±)-6-benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (4 g, 13.41 mmol) was dissolved in MeOH (50 mL). To this solution, $(Boc)_2O$ (5.27 g, 24.13 mmol) and Pd-C (2.85 g, 2.68 mmol) were added at RT. The reaction was stirred at RT for 10 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (100 mL). The filtrate was concentrated under reduced pressure. The residue was triturated with hexane (3 x 20 mL), and the supernatant layer was decanted. The residue was dried under vacuum to obtain crude (±)-*tert*-butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (3.8 g, 87% yield). This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 (d, J = 7.0 Hz, 1H), 6.01 (d, J = 7.1 Hz, 1H), 5.06 - 4.80 (m, 1H), 4.23 - 3.92 (m, 1H), 3.52 - 3.32 (m, 2H), 3.29 - 3.20 (m, 1H), 3.12 - 3.01 (m, 1H), 2.73 - 2.57 (m, 1H), 2.49 - 2.45 (m, 1H), 1.95 - 1.74 (m, 1H), 1.47 - 1.36 (m, 12H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.31 min, m/z = 309.2 $[M+H]^+$, 94.28%.

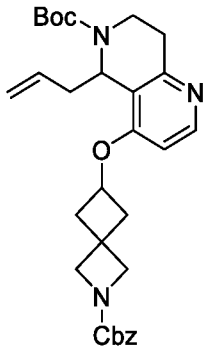
Step 2. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 39, step 3, starting with 1.5 equivalents of benzyl 6-iodo-2-

azaspiro[3.3]heptane-2-carboxylate and 1 equivalent of (±)-*tert*-butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a gummy liquid. Yield: 61.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (br d, J = 5.4 Hz, 1H), 7.43 - 7.28 (m, 5H), 6.70 (d, J = 5.6 Hz, 1H), 5.23 - 5.06 (m, 1H), 5.03 (br s, 2H), 4.83 - 4.70 (m, 1H), 4.44 – 4.30 (m, 1H), 4.19 - 3.87 (m, 5H), 3.58 - 3.39 (m, 2H), 3.27 - 3.13 (m, 1H), 2.90 - 2.69 (m, 4H), 2.37 - 2.14 (m, 2H), 1.86 - 1.70 (m, 1H), 1.68 - 1.38 (m, 12H); LCMS (Method G): Rt = 1.90 min, m/z = 538.3 $[M+H]^+$, 85.43%.

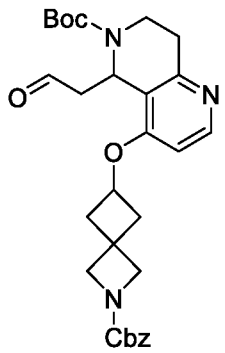
Step 3. (±)-tert-Butyl 5-allyl-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.5 g, 2.79 mmol) in THF (15 mL), 2-nitrophenyl selenocyanate (3.17 g, 13.95 mmol) and tributylphosphine (3.44 mL, 13.95 mmol) were added at 0 °C. The reaction was stirred at the same temperature for 3 h. Hydrogen peroxide (2.75 mL, 27.9 mmol, 30% in H_2O) was added to this reaction mixture at 0 °C, and the reaction was continued at RT for 10 h. After completion, the reaction was quenched with saturated $NaHCO_3$ solution (30 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (30 mL), dried over sodium sulfate, and filtered, and the filtrate was

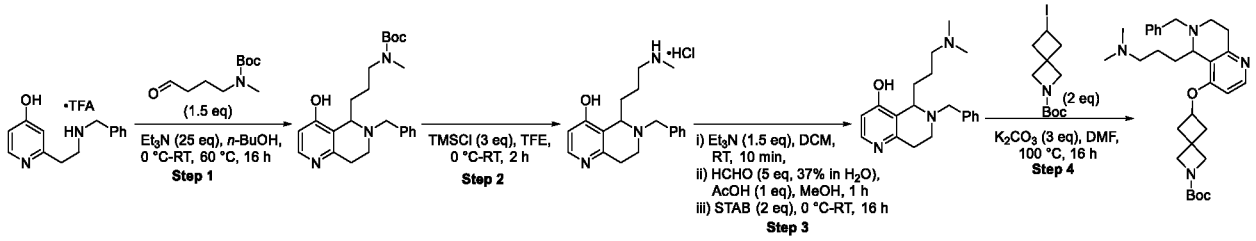
concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 5-allyl-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (910 mg, 57.0% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (br d, J = 5.3 Hz, 1H), 7.43 - 7.26 (m, 5H), 6.72 (d, J = 5.6 Hz, 1H), 5.89 - 5.69 (m, 1H), 5.29 - 5.12 (m, 1H), 5.11 - 4.92 (m, 4H), 4.84 - 4.67 (m, 1H), 4.21 - 3.84 (m, 5H), 3.27 - 3.16 (m, 1H), 2.88 - 2.69 (m, 4H), 2.43 - 2.14 (m, 4H), 1.39 (br s, 9H); LCMS (Method G): Rt = 2.55 min, m/z = 520.3 $[M+H]^+$, 90.75%.

Step 4. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-oxoethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

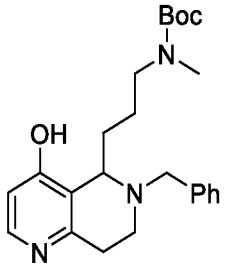


To a stirred solution of (±)-*tert*-butyl 5-allyl-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (700 mg, 1.347 mmol) in THF:H_2O (1:3, 20 mL), osmium tetroxide (1.057 mL, 0.135 mmol, 4 wt% in H_2O) and sodium periodate (720 mg, 3.37 mmol) were added at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with saturated $NaHCO_3$ solution (15 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-oxoethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (650 mg, 53.6% yield) as a gummy liquid. This material was used without further purification. LCMS (Method G): Rt = 2.09 min, m/z = 522.1 $[M+H]^+$, 57.91%.

Intermediate 63. (±)-*tert*-Butyl 6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

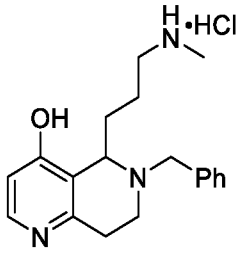


Step 1. (±)-tert-Butyl (3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propyl)(methyl)carbamate



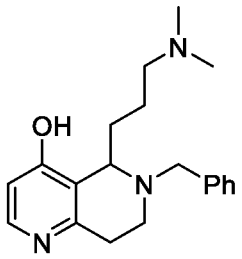
In a 100 mL round bottom flask under a nitrogen atmosphere, 2-(2-(benzylamino)ethyl)pyridin-4-ol trifluoro acetic acid (10.8 g, 33.1 mmol) was dissolved in *n*-butanol (60 mL). To this solution, triethylamine (115 mL, 827 mmol) and *tert*-butyl methyl(4-oxobutyl)carbamate (9.99 g, 49.6 mmol) were added and the reaction was stirred at 60 °C for 16 h. After completion, the reaction was cooled to RT, quenched with saturated sodium bicarbonate solution (30 mL), and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5-11% MeOH in DCM) to obtain (±)-*tert*-butyl (3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propyl)(methyl)carbamate (11 g, 74.6% yield) as semi-solid. LCMS (Method G): Rt = 2.23 min, m/z = 412.3 $[M+H]^+$, 92.43%.

Step 2. (±)-6-Benzyl-5-(3-(methylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with 1 equivalent of (±)-*tert*-butyl (3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propyl)(methyl)carbamate. After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc (3 x 80 mL). The EtOAc layer was decanted, the solid was concentrated under reduced pressure to obtain crude (±)-6-benzyl-5-(3-(methylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride (5 g, quantitative yield) as a solid. This material was used without further purification.

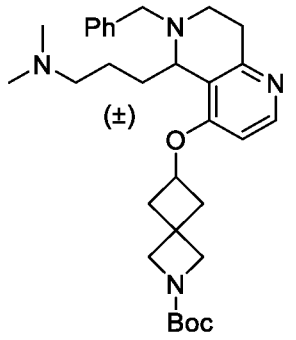
Step 3. (±)-6-Benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with (±)-6-benzyl-5-(3-(methylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride, except that 1.5 equivalents of TEA, 5 equivalents of formaldehyde (37% in H_2O), and 2 equivalents of STAB were used. After completion, the reaction was concentrated under reduced pressure and quenched with sodium bicarbonate solution (50 mL). The mixture was extracted with 10% MeOH in DCM (3 x 70 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (2 g, 42.1%

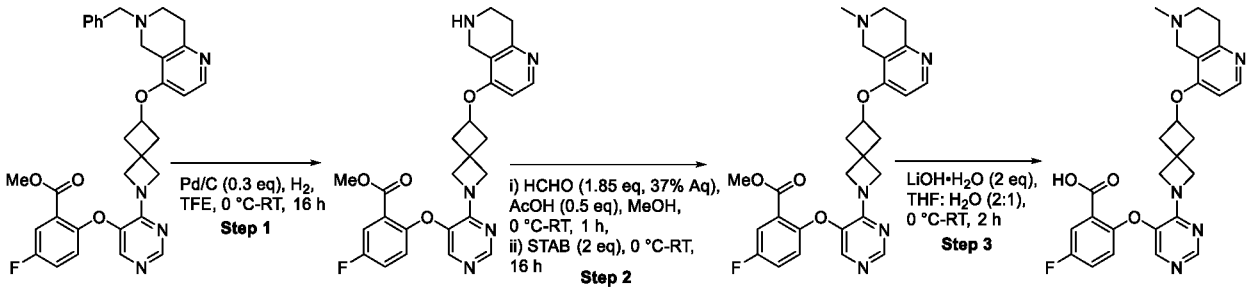
yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.34 (br s, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.36 - 7.32 (m, 4H), 7.31 - 7.25 (m, 1H), 6.10 (d, J = 7.1 Hz, 1H), 3.72 (d, J = 13.0 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.42 - 3.37 (m, 1H), 3.20 - 3.10 (m, 1H), 2.91 - 2.82 (m, 2H), 2.82 - 2.73 (m, 2H), 2.69-2.63 (m, 1H), 2.61 (m, 6H), 1.81 - 1.69 (m, 1H), 1.62 - 1.54 (m, 1H), 1.52 - 1.44 (m, 2H); LCMS (Method G): Rt = 1.31 min, m/z = 326.3 $[M+H]^+$, 98.38%.

Step 4. (±)-tert-Butyl 6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

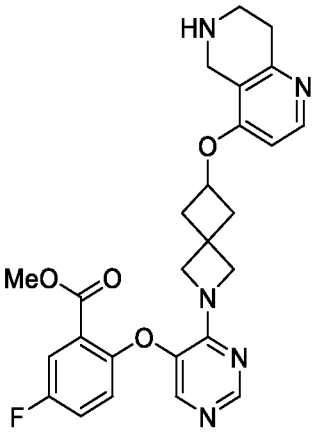


This compound was synthesized following the procedure described for the synthesis of Intermediate 39, step 3, starting with 1 equivalent of (±)-6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol, except that 2 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate was used. After completion, the reaction was cooled to RT, diluted with cold water (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1.5 g, 41.8% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, J = 5.5 Hz, 1H), 7.34 - 7.30 (m, 4H), 7.29 - 7.23 (m, 1H), 6.66 (d, J = 5.7 Hz, 1H), 4.75 - 4.67 (m, 1H), 3.94 - 3.77 (m, 4H), 3.73 - 3.64 (m, 2H), 3.50 (d, J = 13.3 Hz, 1H), 3.26 - 3.16 (m, 2H), 2.98 - 2.80 (m, 2H), 2.77 - 2.66 (m, 2H), 2.19 -2.02 (m, 4H), 2.06 (s, 6H), 1.60 - 1.51 (m, 4H), 1.37 (s, 9H); LCMS (Method G): Rt = 2.08 min, m/z = 521.4 $[M+H]^+$, 89.16%.

Intermediate 64. 5-Fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid



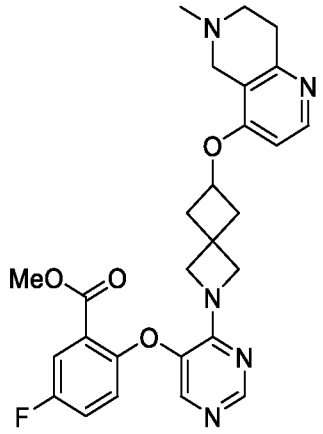
Step 1. Methyl 5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate



This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of methyl 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate, except that 0.3 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to obtain crude methyl 5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate as a solid. This material was used without further purification.

Yield: 97%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.70 - 7.64 (m, 2H), 7.49 (ddd, J = 3.3, 7.9, 9.0 Hz, 1H), 7.10 (dd, J = 4.5, 9.1 Hz, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.73 (quin, J = 6.6 Hz, 1H), 4.31 - 4.15 (m, 4H), 3.82 (s, 3H), 3.72 (s, 2H), 2.98 (t, J = 5.8 Hz, 2H), 2.83 - 2.74 (m, 2H), 2.70 (br t, J = 5.7 Hz, 2H), 2.30 - 2.18 (m, 2H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.56 min, m/z = 492.2 $[M+H]^+$, 97.21%.

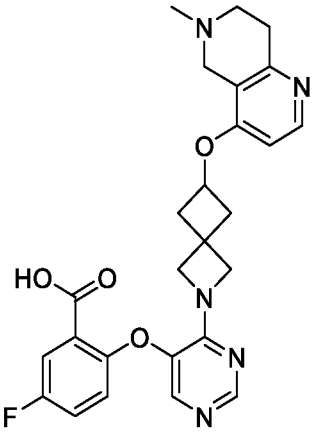
Step 2. Methyl 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate



This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of methyl 5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate and 5 equivalents of formaldehyde (37% aqueous), except that 2 equivalents of STAB and 0.5 equivalent of AcOH were used, and MeOH was used as a solvent. After completion, the reaction was concentrated under reduced pressure. Saturated sodium bicarbonate solution was added to the residue and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to afford methyl 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate as a solid.

Yield: 75%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.69 - 7.65 (m, 2H), 7.49 (ddd, J = 3.3, 7.8, 9.1 Hz, 1H), 7.11 (dd, J = 4.4, 9.1 Hz, 1H), 6.67 (d, J = 5.8 Hz, 1H), 4.75 (quin, J = 6.7 Hz, 1H), 4.27 (s, 2H), 4.18 (s, 2H), 3.82 (s, 3H), 3.35 (s, 2H), 2.84 - 2.76 (m, 4H), 2.65 - 2.59 (m, 2H), 2.36 (s, 3H), 2.30 - 2.23 (m, 2H); LCMS (Method G): Rt = 1.69 min, m/z = 506.3 $[M+H]^+$, 96.85%.

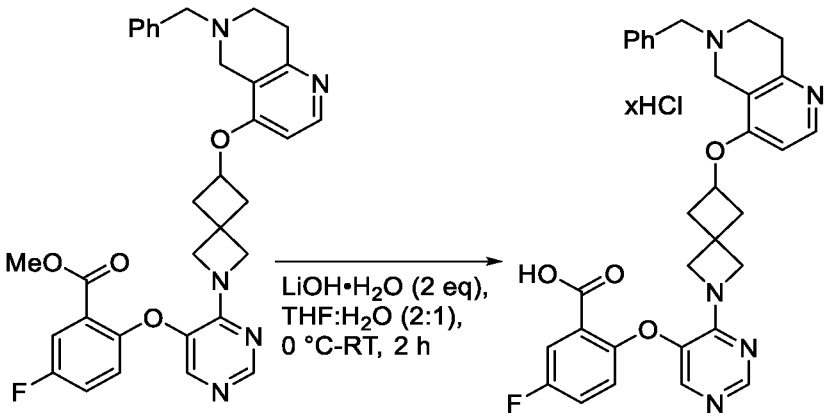
Step 3. 5-Fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid



This compound was synthesized following the procedure described for the synthesis of Example 9, step 2, starting with 1 equivalent of methyl 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate, except that 2 equivalents of $LiOH.H_2O$ was used, and 2:1 THF/H_2O was used as solvent. The organic solvent was removed under reduced pressure. The aqueous layer was acidified with 1.5 N HCl (pH~2) and the solvent was concentrated under reduced pressure. The crude was azeotroped with toluene. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid as a solid.

Yield: 96%; LCMS (Method G): Rt = 1.18 min, m/z = 492.2 $[M+H]^+$, 96.45%.

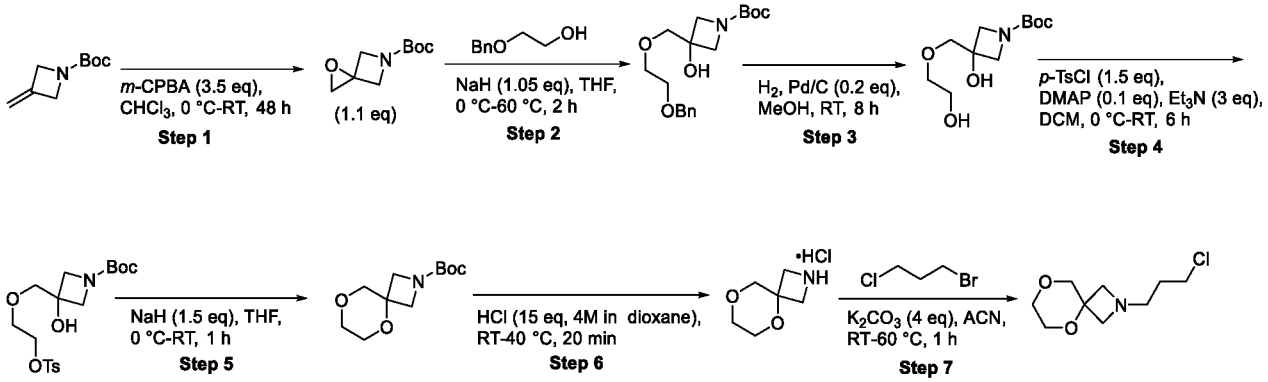
Intermediate 65. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl



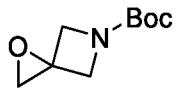
Lithium hydroxide monohydrate (2.164 g, 51.6 mmol) was added to a stirred solution of methyl 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate (15 g, 25.8 mmol) in a mixture of THF (150 mL) and water (75 mL) at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was acidified with 1.5 N HCl (pH-2-3). The mixture was concentrated under reduced pressure and azeotroped with toluene (2 x 50 mL), and then with EtOAc (50 mL), to obtain crude 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl (12 g, 82 % yield) as a solid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 8.19 (d, J = 5.8 Hz, 1H), 7.62 (dd, J = 3.3, 8.8 Hz, 1H), 7.59 (s, 1H), 7.48 - 7.39 (m, 1H), 7.38 - 7.31 (m, 4H), 7.31 - 7.24 (m, 1H), 7.09 (dd, J = 4.5, 9.0 Hz, 1H), 6.68 (d, J = 5.8 Hz, 1H), 4.73 (quin, J = 6.7 Hz, 1H), 4.27 (br s, 2H), 4.17 (br s, 2H), 3.70 (s, 2H), 3.48 (s, 2H), 2.85 - 2.66 (m, 6H), 2.26 - 2.14 (m, 2H), acidic protons were not observed; LCMS (Method G): Rt = 1.37 min, m/z = 568.2 $[M+H]^+$, 99.28%.

Intermediate 66. 2-(3-Chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane



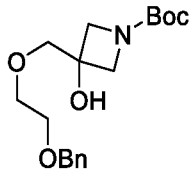
Step 1. tert-Butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate



In a dried, 1000 mL two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-methyleneazetidine-1-carboxylate (4 g, 23.64 mmol) was added in $CHCl_3$ (200 mL). To this solution, *m*-CPBA (20.39 g, 83 mmol) was added at 0 °C and the reaction was stirred at RT for 48 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ solution (200 mL), and the mixture was extracted with EtOAc (100 mL). The organic layer was washed with brine solution (70 mL), dried over sodium sulfate, and filtered, and the filtrate

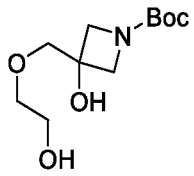
was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 16% EtOAc in hexane) to obtain *tert*-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (1.2 g, 27.4% yield) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 – 4.24 (m, 2H), 4.32 – 4.18 (m, 2H), 2.87 (s, 2H), 1.48 (s, 9H).

Step 2. tert-Butyl 3-((2-(benzyloxy)ethoxy)methyl)-3-hydroxyazetidine-1-carboxylate



In a dried, 100 mL two neck round bottom flask under a nitrogen atmosphere, 2-(benzyloxy)ethan-1-ol (0.900 g, 5.91 mmol) was added in THF (15 mL). To this solution, NaH (0.248 g, 6.21 mmol) was added at 0 °C and the mixture was stirred for 20 min at the same temperature. To this reaction, *tert*-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (1.205 g, 6.50 mmol, in 7 mL THF) was added at 0 °C and the reaction mixture was stirred at 60 °C for 2 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with water (30 mL), and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain *tert*-butyl 3-((2-(benzyloxy)ethoxy)methyl)-3-hydroxyazetidine-1-carboxylate (1.3 g, 60.2% yield) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.30 (m, 5H), 4.58 (s, 2H), 3.92 - 3.81 (m, 4H), 3.77 (dd, J = 3.6, 5.6 Hz, 2H), 3.69 (s, 2H), 3.66 (dd, J = 3.6, 5.6 Hz, 2H), 1.46 (s, 9H), one proton is merged with solvent peaks; LCMS (Method L): Rt = 1.83 min, m/z = 238.1 [M-100+H]$^+$, 92.40%.

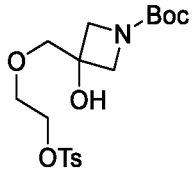
Step 3. tert-Butyl 3-hydroxy-3-((2-hydroxyethoxy)methyl)azetidine-1-carboxylate



In a 100 mL two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-((2-(benzyloxy)ethoxy)methyl)-3-hydroxyazetidine-1-carboxylate (1.3 g, 3.85 mmol) was added in MeOH (20 mL). To this solution, Pd-C (0.820 g, 0.771 mmol) was added at RT. The reaction was stirred at RT for 8 h under a hydrogen atmosphere (balloon pressure). The

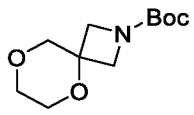
reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 3-hydroxy-3-((2-hydroxyethoxy)methyl)azetidine-1-carboxylate (900 mg, 94% yield) as a viscous liquid. This material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 4H), 3.82 - 3.78 (m, 2H), 3.71 - 3.67 (m, 4H), 1.46 (s, 9H), two protons merged with solvent peaks; LCMS-ELSD (Method G): Rt = 1.42 min, m/z = 248.0 $[M+H]^+$, 99.88%.

Step 4. tert-Butyl 3-hydroxy-3-((2-(tosyloxy)ethoxy)methyl)azetidine-1-carboxylate



In a dried, 100 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-hydroxy-3-((2-hydroxyethoxy)methyl)azetidine-1-carboxylate (900 mg, 3.64 mmol) was added in DCM (20 mL). To this solution, TEA (1.535 mL, 10.92 mmol), DMAP (44.5 mg, 0.364 mmol), and *p*-TsCl (1041 mg, 5.46 mmol) were added at 0 °C. The reaction was stirred at RT for 6 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine solution (30 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 50% EtOAc in hexane) to obtain *tert*-butyl 3-hydroxy-3-((2-(tosyloxy)ethoxy)methyl)azetidine-1-carboxylate (1.2 g, 79% yield) as a gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.26 - 4.20 (m, 2H), 3.88 - 3.78 (m, 4H), 3.78 - 3.74 (m, 2H), 3.61 (s, 2H), 2.48 (s, 3H), 1.46 (s, 9H), one proton merged with solvent peaks; LCMS (Method L): Rt = 1.88 min, m/z = 302.1 $[M-100+H]^+$, 96.56%.

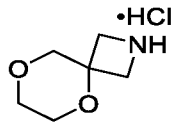
Step 5. tert-Butyl 5,8-dioxa-2-azaspiro[3.5]nonane-2-carboxylate



In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-hydroxy-3-((2-(tosyloxy)ethoxy)methyl)azetidine-1-carboxylate (1.0 g, 2.491 mmol) was added in THF (15 mL). To this solution, NaH (0.149 g, 3.74 mmol) was added at 0 °C and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (50% EtOAc in hexane).

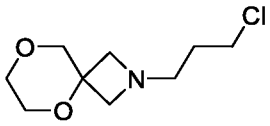
After completion, the reaction was quenched with water (10 mL) and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine solution (20 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain *tert*-butyl 5,8-dioxa-2-azaspiro[3.5]nonane-2-carboxylate (500 mg, 85% yield) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 - 3.80 (m, 4H), 3.73 (s, 2H), 3.72 - 3.65 (m, 4H), 1.46 (s, 9H); LCMS-ELSD (Method B): Rt = 1.71 min, m/z = 130.3 $[M-100+H]^+$, 97.63%.

Step 6. 5,8-Dioxa-2-azaspiro[3.5]nonane hydrochloride



In a 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 5,8-dioxa-2-azaspiro[3.5]nonane-2-carboxylate (400 mg, 1.745 mmol) was added in DCM (2 mL). To this solution, HCl (6.54 mL, 26.2 mmol, 4M in 1,4-dioxane) was added at RT and the reaction was stirred at 40 °C for 20 min. The reaction progress was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to obtain crude 5,8-dioxa-2-azaspiro[3.5]nonane hydrochloride (289 mg, quantitative yield) as a solid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (br s, 2H), 3.87 (br s, 4H), 3.75 (s, 2H), 3.69 - 3.63 (m, 2H), 3.60 - 3.53 (m, 2H).

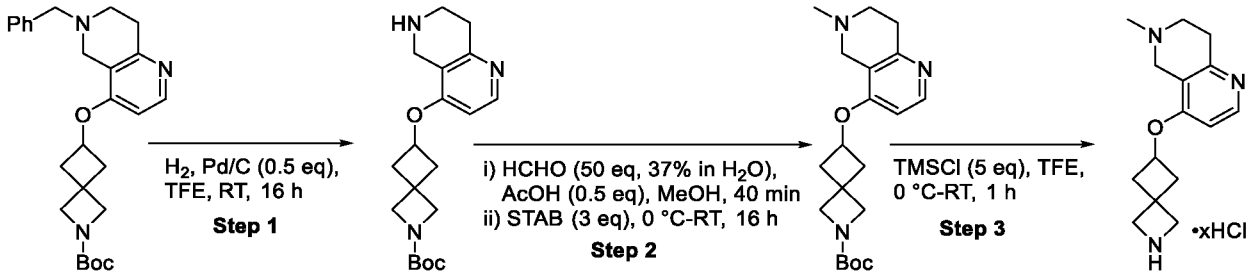
Step 7. 2-(3-Chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane



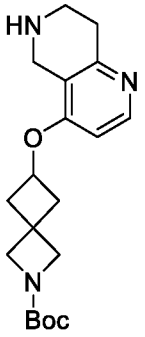
In a 40 mL pressure vial, 5,8-dioxa-2-azaspiro[3.5]nonane hydrochloride (285 mg, 1.721 mmol) was added in ACN (10 mL). To this solution, 1-bromo-3-chloropropane (257 mg, 1.635 mmol) and K_2CO_3 (951 mg, 6.88 mmol) were added at RT and the reaction was stirred at 60 °C for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (30 mL) and the mixture was extracted with EtOAc (2 x 40 mL). The combined organic layer was washed with brine solution (20 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to afford crude 2-(3-chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane (240 mg, 67.8 % yield) as a liquid. This material was used without further purification. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 3.78 (s, 2H), 3.67 (s, 4H), 3.59 (t, *J* = 6.5 Hz, 2H), 3.48 - 3.42 (m, 2H), 2.94 - 2.88 (m, 2H), 2.65 (t, *J* = 6.9 Hz, 2H), 1.84 (quin, *J* = 6.8 Hz, 2H).

Intermediate 67. 4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine xHCl

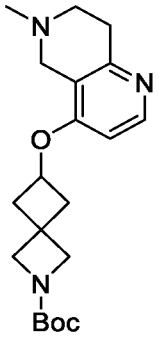


Step 1. tert-Butyl 6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



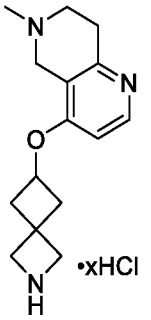
In a dried, 1 L round bottom flask under a nitrogen atmosphere, *tert*-butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (25 g, 57.4 mmol) was dissolved in TFE (250 mL). Pd-C (30.5 g, 28.7 mmol) was added to this solution, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 10% MeOH in DCM (3 x 250 mL). The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (24 g, 98% yield) as a semi-solid. LCMS (Method G): Rt = 1.56 min, m/z = 346.1 $[M+H]^+$, 81.05%. This material was used without further purification.

Step 2. tert-Butyl 6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



In a 1 L two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (24 g, 69.5 mmol) was dissolved in MeOH (50 mL). To this solution, formaldehyde (96 mL, 3474 mmol, 37% in H_2O) and acetic acid (1.989 mL, 34.7 mmol) were added at 0 °C, and the reaction was stirred at RT for 40 min. To this reaction mixture, sodium triacetoxyborohydride (53.4 g, 252 mmol) was added at 0 °C, and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain *tert*-butyl 6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (17.5 g, 67.4%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (d, J = 5.6 Hz, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.71 (quin, J = 6.8 Hz, 1H), 3.91 (br s, 2H), 3.83 (br s, 2H), 3.37 (br s, 2H), 2.85 - 2.79 (m, 2H), 2.77 - 2.72 (m, 2H), 2.69 - 2.63 (m, 2H), 2.38 (s, 3H), 2.27 - 2.17 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 1.75 min, m/z = 360.1 $[M+H]^+$, 96.19%.

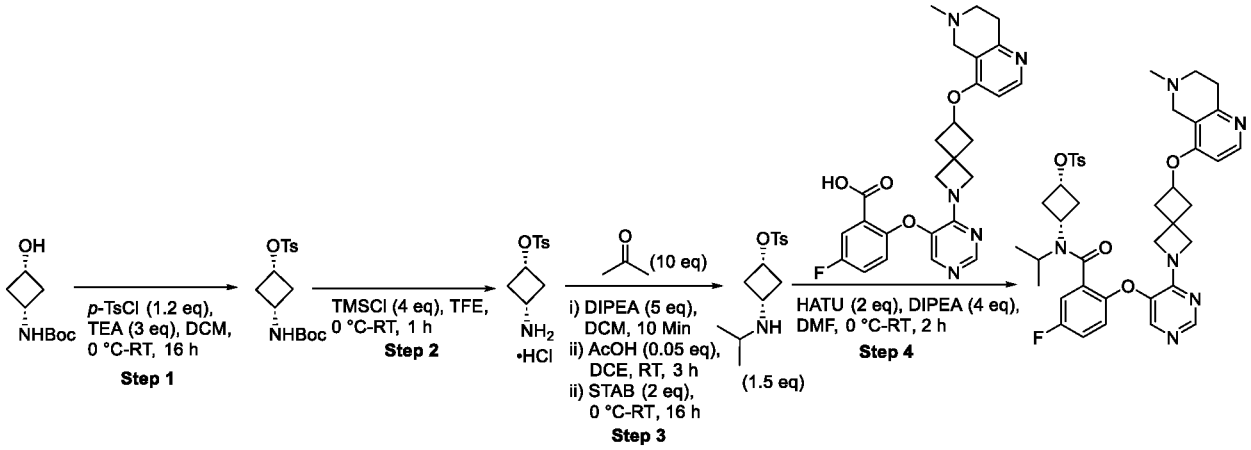
Step 3. 4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine xHCl



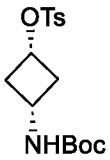
To a stirred solution of *tert*-butyl 6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (600 mg, 1.669 mmol) in TFE (7 mL), TMSCl (1.067 mL, 8.35 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under

reduced pressure and the residue was triturated with EtOAc (3 x 10 mL). The organic layer was decanted, and the residue was dried under reduced pressure to afford crude 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine xHCl as a solid (300 mg, 69.35% yield). This material was used without further purification. LCMS (Method G): Rt = 1.08 min, m/z = 260.0 $[M+H]^+$, 92.94%.

Intermediate 68. (1*s*,3*s*)-3-(5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamido)cyclobutyl 4-methylbenzenesulfonate

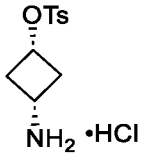


Step 1. (1s,3S)-3-((tert-Butoxycarbonyl)amino)cyclobutyl 4-methylbenzenesulfonate



To a stirred solution of *tert*-butyl (1*s*,3*s*)-3-hydroxycyclobutyl)carbamate (2 g, 10.68 mmol) in DCM (10 mL), TEA (0.962 mL, 6.90 mmol) was added at 0 °C. To this reaction mixture, *p*-TsCl (526 mg, 2.76 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ solution (25 mL), and the mixture was extracted with DCM (3 x 35 mL). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain (1*s*,3*s*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl 4-methylbenzenesulfonate (2.5 g, 68.4% yield) as a solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 - 7.77 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.65 (brs, 1H), 4.51 (quin, *J* = 7.2 Hz, 1H), 3.86 - 3.64 (m, 1H), 2.76 - 2.66 (m, 2H), 2.47 (s, 3H), 2.08 - 1.96 (m, 2H), 1.43 (s, 9H).

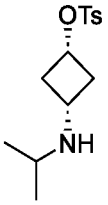
Step 2. (1s,3s)-3-Aminocyclobutyl 4-methylbenzenesulfonate hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with 1 equivalent of (1*s*,3*s*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl 4-methylbenzenesulfonate. After completion, the reaction was concentrated under reduced pressure, triturated with EtOAc, and the organic layer was decanted. The residue was concentrated under reduced pressure to afford crude (1*s*,3*s*)-3-aminocyclobutyl 4-methylbenzenesulfonate hydrochloride as a solid.

Yield: 98.2%; LCMS (Method G): Rt = 1.44 min, m/z = 242.1 $[M+H]^+$, 99.34%. This material was used without further purification.

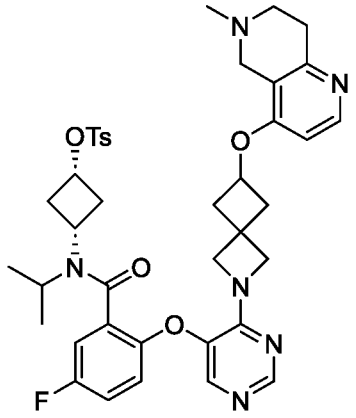
Step 3. (1s,3s)-3-(Isopropylamino)cyclobutyl 4-methylbenzenesulfonate



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (1*s*,3*s*)-3-aminocyclobutyl 4-methylbenzenesulfonate hydrochloride and 10 equivalents of acetone, except that 5 equivalents of DIPEA, 0.05 equivalent of AcOH and 2 equivalents of STAB were used, and DCM was used as a solvent. After completion, the reaction was quenched with water and the mixture was extracted with DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude (1*s*,3*s*)-3-(isopropylamino)cyclobutyl 4-methylbenzenesulfonate as a semi-solid.

Yield: 58.8%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 - 7.78 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.55 (quin, *J* = 7.4 Hz, 1H), 2.95 - 2.86 (m, 1H), 2.84 - 2.74 (m, 1H), 2.69 - 2.60 (m, 2H), 2.47 (S, 3H), 1.93 - 1.82 (m, 2H), 1.01 (d, *J* = 6.3 Hz, 6H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.75 min, m/z = 284.1 $[M+H]^+$; 69.32%. This material was used without further purification.

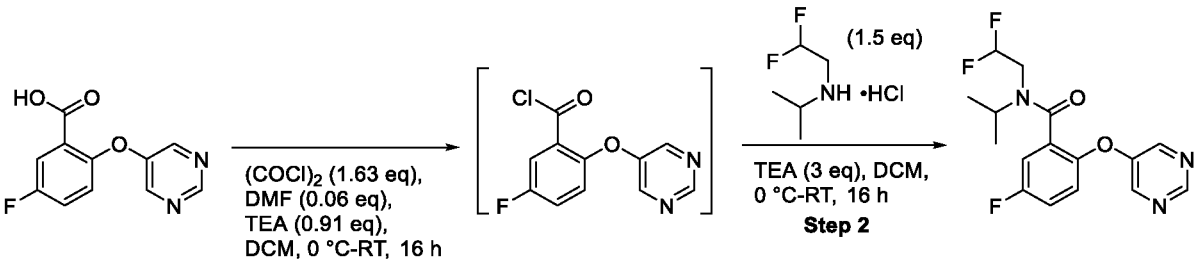
Step 4. *(1s,3s)-3-(5-Fluoro-N-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamido)cyclobutyl 4-methylbenzenesulfonate*



This compound was synthesized following the procedure described for the synthesis of Example 434, step 2, starting with 1 equivalent of 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid, except that 1.5 equivalents of (1*s*,3*s*)-3-(isopropylamino)cyclobutyl 4-methylbenzenesulfonate, 2 equivalents of HATU and 4 equivalents of DIPEA were used. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (1*s*,3*s*)-3-(5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamido)cyclobutyl 4-methylbenzenesulfonate as a solid.

Yield: 70.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.79 - 7.72 (m, 3H), 7.45 (d, J = 7.8 Hz, 2H), 7.32 - 7.21 (m, 2H), 7.15 - 7.00 (m, 1H), 6.69 - 6.65 (m, 1H), 4.79 - 4.69 (m, 1H), 4.61 - 4.41 (m, 1H), 4.30 - 4.03 (m, 4H), 3.81 - 3.52 (m, 2H), 3.37 (br s, 2H), 3.28 - 3.18 (m, 1H), 2.86 - 2.72 (m, 4H), 2.69 - 2.60 (m, 2H), 2.40 (s, 3H), 2.36 (s, 3H), 2.34 - 2.18 (m, 5H), 1.40 – 0.91 (m, 6H); LCMS (Method G): Rt = 2.00 min, m/z = 757.1 $[M+H]^+$; 98.94%; Chiral SFC (Method AAZ): Rt = 3.99 min, 100%.

Intermediate 69. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide

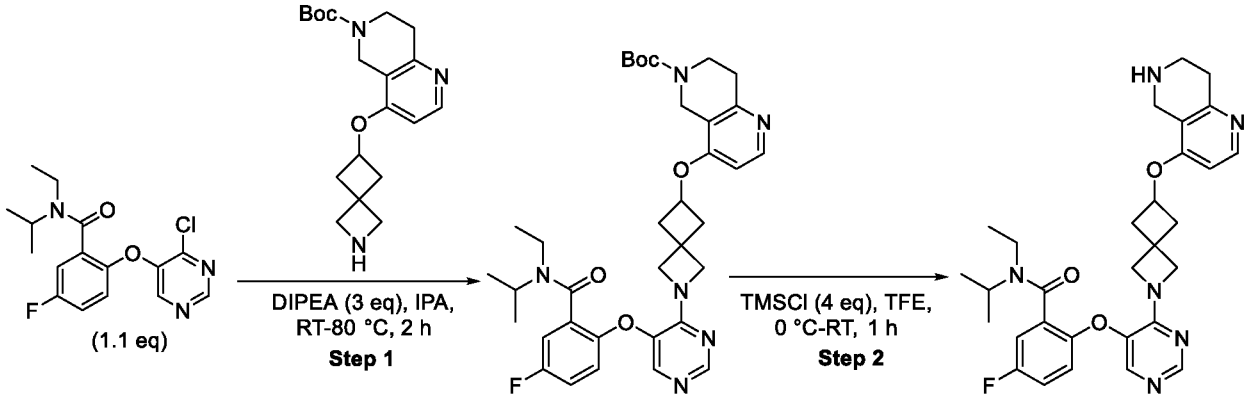


A 500 L, glass-jacketed reactor was placed under a nitrogen atmosphere and connected to a 2 N NaOH scrubber. The flask was charged with DCM (100 mL), and 5-fluoro-2-(pyrimidin-5-

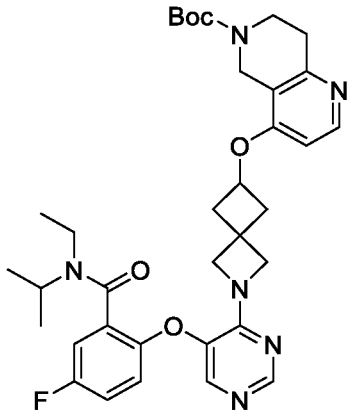
yloxy)benzoic acid was added (16.70 kg, 61.8 moles) (solid was difficult to dissolve) at 20-30 °C. To this stirred suspension, DMF (271 g, 3.72 moles) was added, followed by oxalyl chloride (1.02 kg, 8.03 moles) dropwise (an exotherm was detected). TEA (5.69 kg, 56.2 moles) was charged to the reaction mixture at 0-5 °C (the solid was almost dissolved). Another lot of oxalyl chloride (11.8 kg, 92.6 moles) was added to the above reaction mixture at 5-10 °C (a large amount of gas was generated). The reaction was stirred at 15-25 °C for 16 h. The batch was sampled for IPC, which indicated 93.5% conversion into acid chloride (an aliquot of the reaction was quenched with MeOH prior to analysis). The reaction was concentrated under reduced pressure at 40-45°C to remove excess oxalyl chloride. DCM (100 L) was charged to the residue, and the solvent was concentrated under reduced pressure (this procedure was repeated three times). In a glass-jacketed reactor, the crude product was dissolved in dry DCM (100 L), and the mixture was charged with *N*-(2,2-difluoroethyl)propan-2-amine hydrochloride (14.8 kg, 24.33 moles). To this mixture, TEA (18.8 kg, 48.68 moles) was added at 0-10 °C, and the reaction was stirred at 15-25 °C for 2 h. The batch was sampled for IPC, which indicated 96.8% conversion to the product. The reaction was cooled to 0-10 °C, the batch was charged with 1 M HCl (66.7 mL) (a large amount of gas was generated), and the mixture was stirred at 20-25 °C for 20 min. The mixture was allowed to stand for 20 min to separate layers. The upper layer was separated, and the bottom layer (organic layer) was transferred to the reactor, and the mixture was cooled to 0-10 °C. A saturated $NaHCO_3$ solution (83.3 L) was charged to the bottom layer (a large amount of gas was generated). The mixture was stirred at 20-25 °C for 20 min and allowed to stand for 20 min to separate layers. The upper layer was separated, and the bottom layer (organic layer) was transferred to the reactor. The mixture was concentrated under reduced pressure. MTBE (100 L) was charged to the residue and the solvent was concentrated under reduced pressure (this procedure was repeated three times). Anhydrous MTBE (100 L) was charged to the residue, and the mixture was filtered through a silica gel bed (10% wt). The bed was washed with MTBE (2 x 20 L). The filtrate was concentrated under reduced pressure (bath temperature ~45 °C) to obtain crude material. The crude was charged with MTBE (35.8 L) and *n*-heptane (53.7 L), and the mixture was stirred at 0-10 °C for 12 h. The mixture was filtered to obtain a wet product. The solid was dried under vacuum to afford *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (19.6 kg, 91.2% yield). HPLC purity: 98.4%.

Synthesis of Compounds

Example 1. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 23)

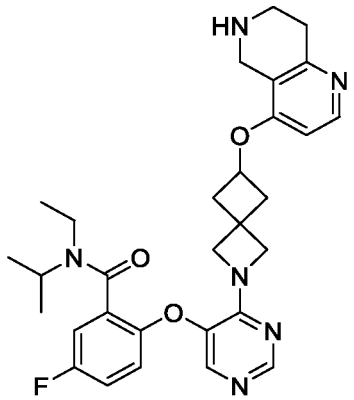


Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



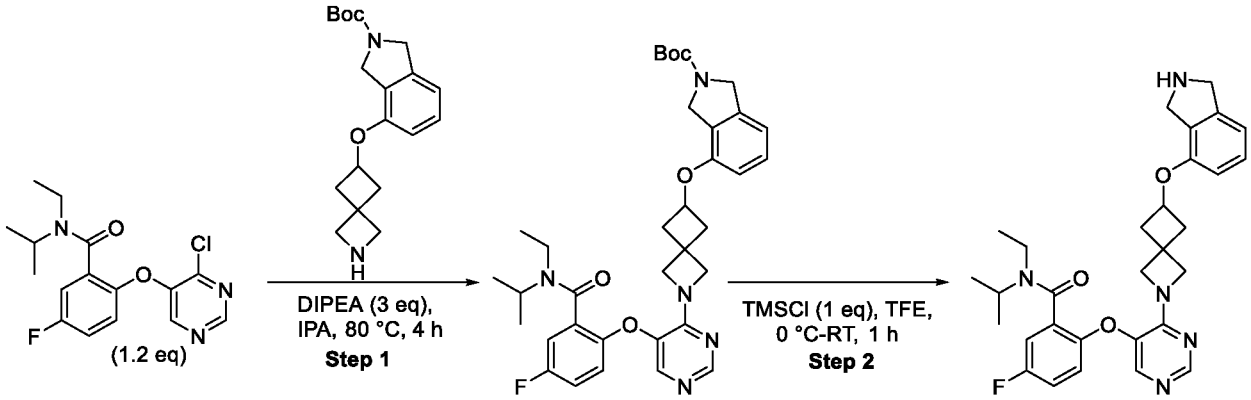
In a 100 mL single neck round bottom flask under nitrogen atmosphere, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (140 mg, 0.414 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (157 mg, 0.456 mmol) were added in 2-propanol (5 mL). To this reaction mixture, DIPEA (0.217 mL, 1.243 mmol) was added at RT, and the reaction was stirred for 2 h at 80 °C. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 5% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (150 mg, 45.4% yield) as a viscous liquid. LCMS (Method D): Rt = 2.07 min, m/z = 647.1 $[M+H]^+$, 81.09%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

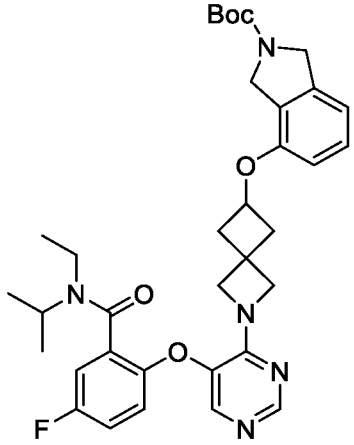


In a 50 mL single neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (150 mg, 0.232 mmol) was added in 2,2,2-trifluoroethanol (3 mL). To this solution, TMSCl (0.119 mL, 0.928 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by Prep HPLC (Method E) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (55 mg, 42.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 - 8.14 (m, 1H), 7.76 - 7.64 (m, 1H), 7.36 - 7.20 (m, 2H), 7.10 - 7.00 (m, 1H), 6.67 - 6.62 (m, 1H), 4.79 - 4.58 (m, 1H), 4.33 - 4.02 (m, 4H), 3.75 (quin, J = 6.7 Hz, 1H), 3.71 - 3.65 (m, 2H), 3.49 - 3.38 (m, 1H), 3.29 - 3.09 (m, 2H), 3.00 - 2.91 (m, 2H), 2.84 - 2.72 (m, 2H), 2.72 - 2.63 (m, 2H), 2.31 - 2.14 (m, 2H), 1.31 - 0.89 (m, 9H); LCMS (Method B): Rt = 0.95 min, m/z = 547.2 $[M+H]^+$; HPLC (Method A): Rt = 4.69 min, 98.90%.

Example 2. *N*-Ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 1)



Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate

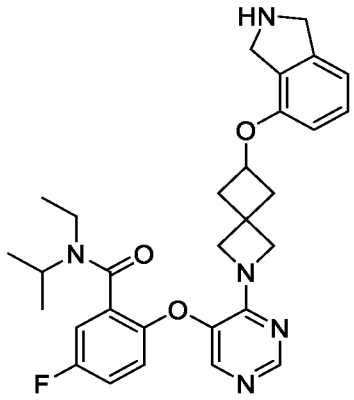


Step 1 was performed in two batches (100 mg and 30 mg batches).

This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 1.2 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide was used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 5% MeOH in DCM) to afford *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate.

Yield: 52%; LCMS (Method D): Rt = 2.36 min, m/z = 632.2 $[M+H]^+$, 68.52%.

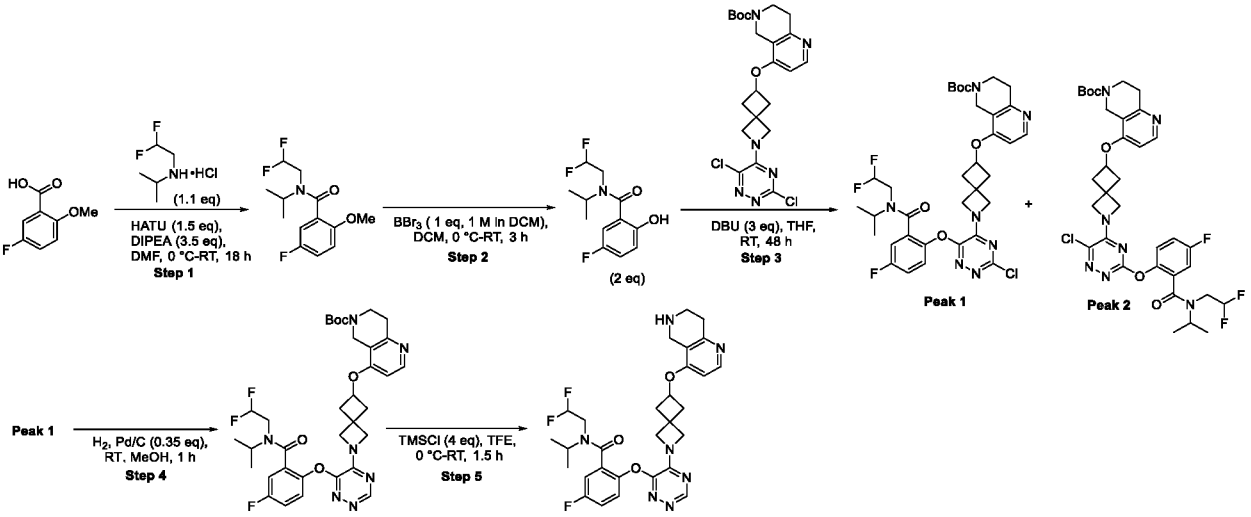
Step 2. N-Ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



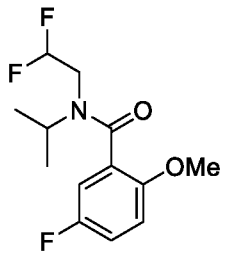
This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting from *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 1 equivalent of TMSCl (22.36 mg, 0.206 mmol) was used. After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride. The crude compound was diluted with EtOAc (20 mL) and washed with $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by Prep HPLC (Method A) to afford *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 40.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 7.79 - 7.63 (m, 1H), 7.34 - 7.18 (m, 2H), 7.16 - 6.99 (m, 2H), 6.90 - 6.79 (m, 1H), 6.74 - 6.58 (m, 1H), 4.75 - 4.60 (m, 1H), 4.59 - 4.36 (m, 1H), 4.34 - 4.07 (m, 4H), 4.06 - 3.93 (m, 3H), 3.81 - 3.67 (m, 1H), 3.48 - 3.38 (m, 1H), 3.27 - 3.09 (m, 2H), 2.87 - 2.70 (m, 2H), 2.31 - 2.14 (m, 2H), 1.32 - 0.95 (m, 9H); LCMS (Method D): Rt = 1.67 min, m/z = 532.1 $[M+H]^+$;
HPLC (Method A): Rt = 5.04 min, 99.67%.

Example 3. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 82)

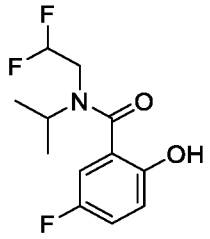


Step 1. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-methoxybenzamide



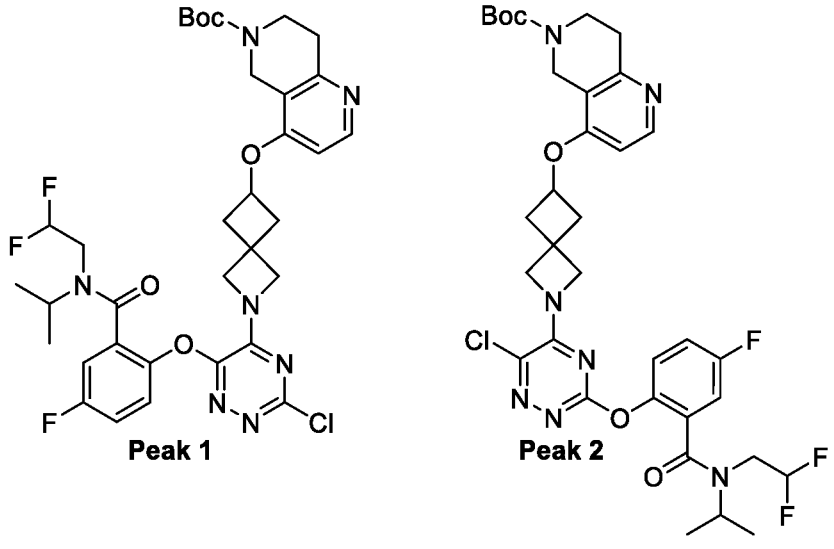
In a 500 mL three neck round bottom flask under a nitrogen atmosphere, 5-fluoro-2-methoxybenzoic acid (10 g, 58.8 mmol) and *N*-(2,2-difluoroethyl)propan-2-amine hydrochloride (10.32 g, 64.7 mmol) were added in DMF (100 mL) at 0 °C. To this reaction mixture, HATU (33.5 g, 88 mmol) and DIPEA (35.8 mL, 206 mmol) were added, and the reaction was stirred at RT for 18 h. The progress of the reaction was monitored by TLC (60% EtOAc in hexane). After completion, the reaction was diluted with ice-cold water (500 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layer was washed with brine solution (300 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 25% EtOAc in hexane) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide (10.8 g, 63.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 – 7.19 (m, 1H), 7.16 – 7.01 (m, 2H), 6.24 (tt, J = 4.3, 56.9 Hz, 1H), 3.78 (s, 3H), 3.82 – 3.61 (m, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H); LCMS (Method H): Rt = 1.91 min, m/z = 276.2 $[M+H]^+$, 95.69%.

Step 2. N-(2,2-Difluoroethyl)-5-fluoro-2-hydroxy-N-isopropylbenzamide



To a stirred solution of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide (10.8 g, 39.2 mmol) in DCM (100 mL), BBr_3 (39.2 mL, 39.2 mmol, 1M in DCM) was added slowly using a dropping funnel at 0 °C. The reaction was slowly warmed to RT and stirred for 3 h. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, diluted with ice-cold water (400 mL), and extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine solution (500 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (10 g, 93% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 7.08 (td, *J* = 3.2, 8.7 Hz, 1H), 6.99 (dd, *J* = 3.2, 8.5 Hz, 1H), 6.87 (dd, *J* = 4.5, 9.0 Hz, 1H), 6.42 – 6.00 (m, 1H), 3.80 – 3.62 (m, 3H), 1.08 (d, *J* = 6.7 Hz, 6H); LCMS (Method D): Rt = 1.67 min, m/z = 262.1 $[M+H]^+$, 95.75%.

Step 3. tert-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

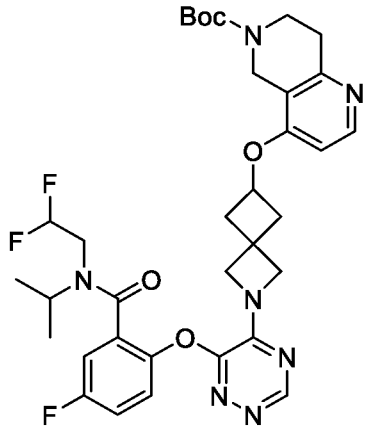


To a stirred solution of *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (847 mg, 3.24 mmol) in THF (30 mL), DBU (0.733 mL, 4.86 mmol) was added at 0 °C. To this reaction mixture, *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (800 mg, 1.621 mmol) was added, and the reaction was stirred at RT for 48 h. The progress of the reaction was monitored by LCMS (Method D). After completion, the reaction was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 100% EtOAc) to obtain the mixture of regioisomers. The mixture was purified by Prep HPLC (Method D) to obtain both isomers.

Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (264 mg, 0.367 mmol, 22.63 % yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 – 8.21 (m, 1H), 7.51 – 7.35 (m, 3H), 6.75 (d, J = 5.8 Hz, 1H), 6.40 – 6.01 (m, 1H), 4.85 – 4.78 (m, 1H), 4.68 – 4.50 (m, 2H), 4.43 – 4.34 (m, 2H), 4.31 – 4.18 (m, 2H), 3.80 – 3.66 (m, 1H), 3.64 – 3.56 (m, 2H), 2.91 – 2.75 (m, 4H), 2.55 (s, 2H), 2.42 – 2.28 (m, 2H), 1.50 – 1.34 (m, 9H), 1.22 – 0.73 (m, 6H); LCMS (Method D): Rt = 2.34 min, m/z = 718.3 $[M+H]^+$; HPLC (Method A): Rt = 6.76 min, 99.84%.

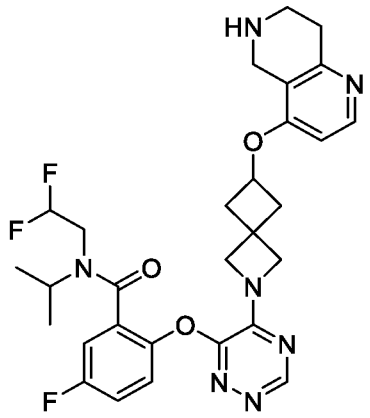
Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (211 mg, 18.01% yield). LCMS (Method G): Rt = 2.24 min, m/z = 718.3 $[M+H]^+$; HPLC (Method A): Rt = 6.89 min, 99.43%.

Step 4. tert-Butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



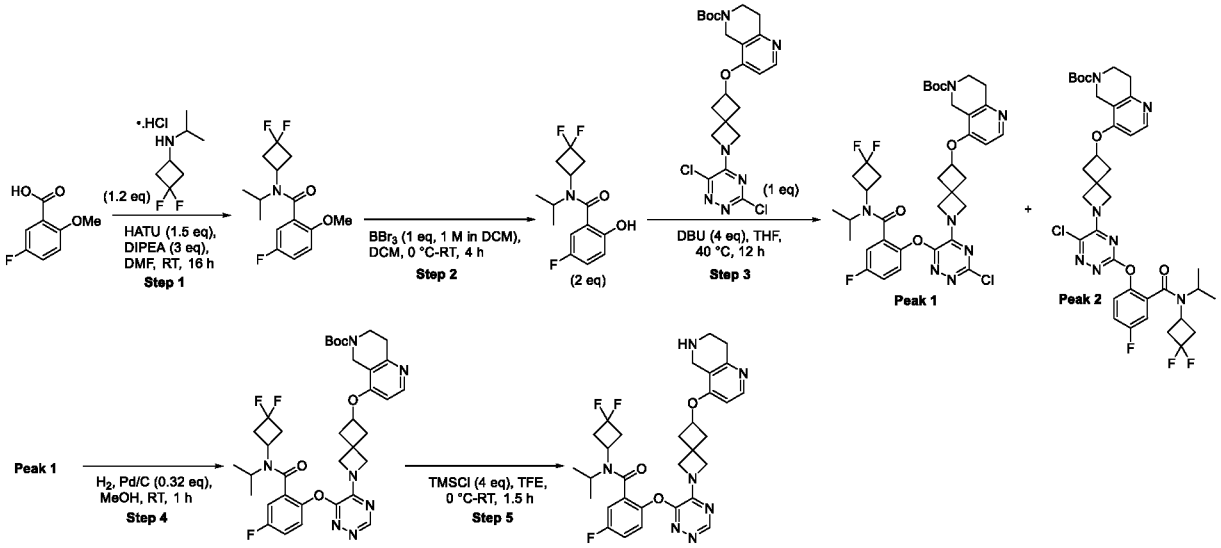
In a 100 mL round bottom flask under argon atmosphere, *tert*-butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.265 g, 0.369 mmol) was dissolved in MeOH (25 mL). To this solution, Pd-C (0.137 g, 0.129 mmol) was added, and the reaction was stirred at RT for 1 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in EtOAc). After completion, the reaction was filtered through a Celite® pad and the pad was washed with MeOH (3 x 25 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.221 g, 79% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.25 (d, J = 5.6 Hz, 1H), 7.55 – 7.32 (m, 3H), 6.77 (d, J = 5.7 Hz, 1H), 6.39 – 5.96 (m, 1H), 4.87 – 4.78 (m, 1H), 4.67 – 4.44 (m, 4H), 4.38 (s, 2H), 4.30 – 4.13 (m, 2H), 3.84 – 3.39 (m, 3H), 2.91 – 2.74 (m, 4H), 2.39 – 2.24 (m, 2H), 1.43 (s, 9H), 1.23 – 0.40 (m, 6H); LCMS (Method G): Rt = 2.00 min, m/z = 684.6 $[M+H]^+$, 99.54%.

Step 5. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

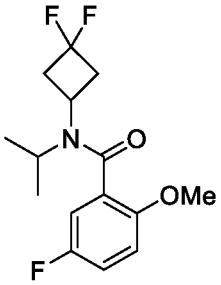


To a stirred solution of *tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.2 g, 0.293 mmol) in 2,2,2-trifluororethanol (4 mL), TMSCl (0.148 mL, 1.170 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (10% MeOH in EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (0.16 g, 84% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.53 – 7.35 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 6.35 – 5.95 (m, 1H), 4.83 – 4.70 (m, 1H), 4.64 – 4.41 (m, 2H), 4.30 – 4.03 (m, 2H), 3.72 (s, 3H), 3.59 – 3.56 (m, 2H), 2.97 (t, J = 5.9 Hz, 2H), 2.81 (br s, 2H), 2.74 – 2.64 (m, 2H), 2.39 – 2.21 (m, 2H), 1.19 – 0.59 (m, 6H); -NH proton was not observed. LCMS (Method B): Rt = 1.44 min, m/z = 584.0 $[M+H]^+$; HPLC (Method A): Rt = 4.76 min, 97.27%.

Example 4. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 172)



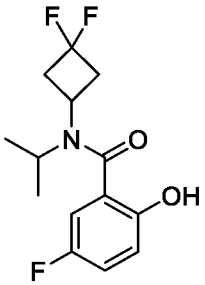
Step 1. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-methoxybenzamide



This compound was synthesized following the procedure described for the synthesis of Example 3, step 1, except that 2 equivalents of DIPEA and 1.2 equivalents of 3,3-difluoro-*N*-isopropylcyclobutan-1-amine hydrochloride were used. The crude compound was purified by silica gel flash column chromatography using 20% EtOAc in hexane to afford *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide.

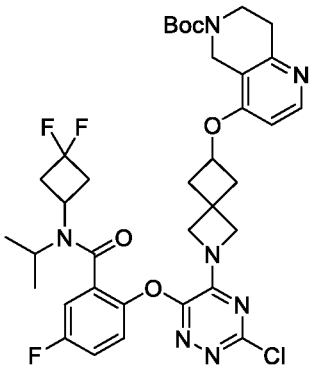
Yield: 87%; LCMS: (Method G): Rt = 1.97 min, m/z= 302.3 $[M+H]^+$; 96.28%.

Step 2. N-(3,3-Difluorocyclobutyl)-5-fluoro-2-hydroxy-N-isopropylbenzamide

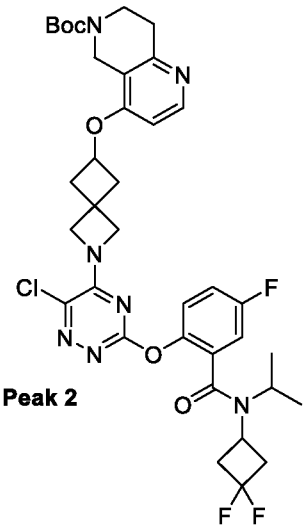


This compound was synthesized following the procedure described for the synthesis of Example 3, step 2. The crude *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide thus obtained was used for the next step without further purification. Yield: 89%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H), 7.07 – 7.01 (m, 1H), 7.00 – 6.93 (m, 1H), 6.89 – 6.81 (m, 1H), 3.99 – 3.84 (m, 1H), 3.78 – 3.42 (m, 3H), 2.80 – 2.62 (m, 2H), 1.12 (br s, 6H); LCMS (Method G): Rt = 1.94 min, m/z = 288.2 $[M+H]^+$; 89.95%.

Step 3. tert-Butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



Peak 1



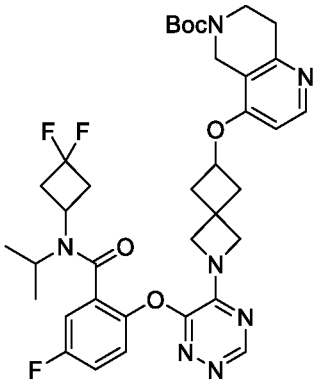
Peak 2

This compound was synthesized following the procedure described for the synthesis of Example 3, step 3, except that 4 equivalents of DBU was used, and the reaction was stirred at 40 °C. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 100% EtOAc) to obtain the mixture of regioisomers. Purification by achiral Prep SFC (Method A) gave *tert*-butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (Peak 1; less polar spot by TLC).

Yield: 39.6%; LCMS (Method G): Rt = 2.26 min, m/z = 744.6 $[M+H]^+$, 98.14%.

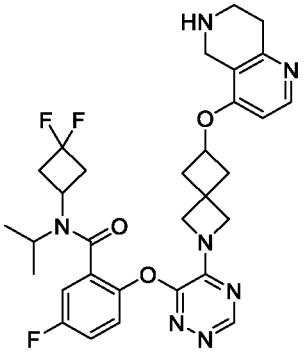
Note: Peak 2 (more polar spot by TLC) was not isolated.

Step 4. tert-Butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 3, step 4, except that 0.32 equivalents of Pd/C was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. Yield: 76%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.25 (d, J = 5.6 Hz, 1H), 7.62 – 7.21 (m, 3H), 6.75 (d, J = 5.6 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.74 – 4.47 (m, 2H), 4.38 (s, 2H), 4.31 – 4.13 (m, 2H), 3.85 (br s, 1H), 3.72 – 3.57 (m, 3H), 3.53 – 3.34 (m, 2H), 2.95 – 2.74 (m, 4H), 2.40 – 2.24 (m, 2H), 1.62 – 1.22 (m, 9H), 1.22 – 0.59 (m, 6H); LCMS (Method F): Rt = 2.30 min, m/z = 710.2 $[M+H]^+$, 97.13%.

Step 5. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

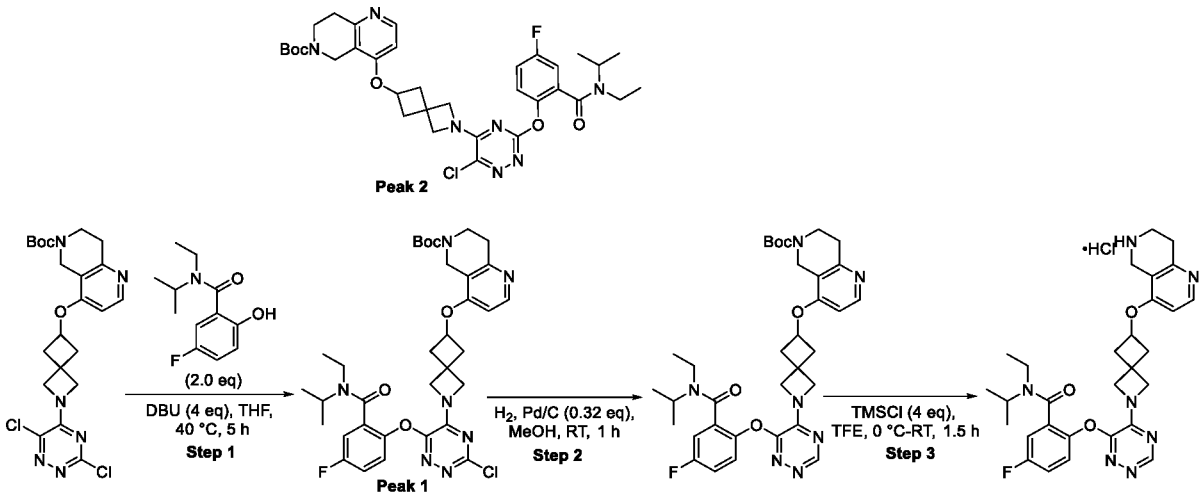


This compound was synthesized following the procedure described for the synthesis of Example 3, step 5. The crude *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride was purified by reverse phase chromatography using a

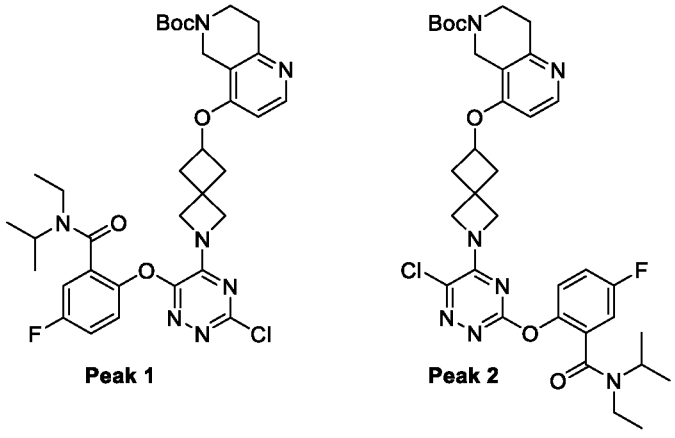
SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

Yield: 85%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.71 – 6.99 (m, 3H), 6.76 (br s, 1H), 4.83 (quin, J = 6.7 Hz, 1H), 4.71 – 4.49 (m, 2H), 4.32 – 4.13 (m, 2H), 3.95 (s, 2H), 3.80 – 3.39 (m, 1H), 3.80 – 3.39 (m, 3H), 3.23 (t, J = 6.1 Hz, 2H), 3.00 – 2.76 (m, 4H), 2.74 – 2.55 (m, 2H), 2.34 – 2.33 (m, 2H), 1.25 – 0.42 (m, 6H).-NH proton was not observed. LCMS (Method B): Rt = 1.55 min, m/z = 610.0 $[M+H]^+$; HPLC (Method A): Rt = 4.96 min, 99.55%.

Example 5. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride (Compound No. 90)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

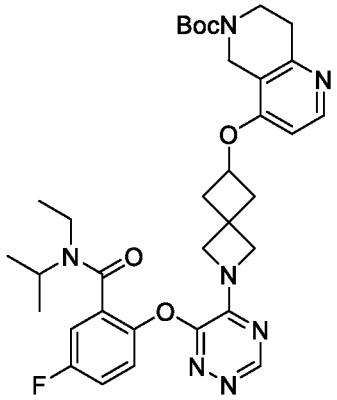


To a stirred solution of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (0.640 g, 2.84 mmol) in THF (15 mL), DBU (0.848 mL, 5.68 mmol) was added at 0 °C under nitrogen atmosphere. To this reaction mixture, *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.701 g, 1.421 mmol) was added under nitrogen atmosphere. The reaction was slowly warmed to RT and stirred at 40 °C for 5 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 100% EtOAc; less polar spot by TLC) to obtain peak 1.

Peak 1 (less polar spot by TLC): *tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.402 g, 39.0% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 - 8.22 (m, 1H), 7.49 - 7.42 (m, 1H), 7.41 - 7.32 (m, 2H), 6.77 - 6.73 (m, 1H), 4.86 - 4.77 (m, 1H), 4.69 - 4.57 (m, 2H), 4.41 - 4.35 (m, 2H), 4.32 - 4.19 (m, 2H), 4.07 - 4.00 (m, 2H), 3.66 - 3.58 (m, 3H), 3.19 - 3.01 (m, 2H), 2.91 - 2.74 (m, 4H), 1.44 – 1.40 (m, 9H), 0.91 - 1.20 (m, 9H); LCMS (Method B): Rt = 2.32 min, m/z = 682.2 $[M+H]^+$, 94.72%.

Peak 2 (more polar spot by TLC) was not isolated.

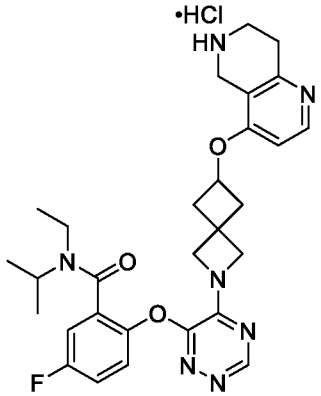
Step 2. tert-Butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 100 mL round bottom flask under argon atmosphere, *tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.35 g, 0.513 mmol) was

dissolved in MeOH (25 mL). To this solution, Pd-C (0.175 g, 0.164 mmol) was added, and the reaction was stirred at RT for 1 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.288 g, 73.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 - 8.44 (m, 1H), 8.28 - 8.22 (m, 1H), 7.49 - 7.41 (m, 1H), 7.39 - 7.31 (m, 2H), 6.78 - 6.75 (m, 1H), 4.87 - 4.78 (m, 1H), 4.67 - 4.50 (m, 2H), 4.40 - 4.36 (m, 2H), 4.32 - 4.13 (m, 2H), 3.67 - 3.58 (m, 3H), 3.46 - 3.36 (m, 1H), 3.14 - 2.98 (m, 1H), 2.90 - 2.76 (m, 4H), 2.40 - 2.27 (m, 2H), 1.42 (s, 9H), 0.66 - 1.16 (m, 9H); LCMS (Method G): Rt = 2.01 min, m/z = 648.6 $[M+H]^+$, 96.56%.

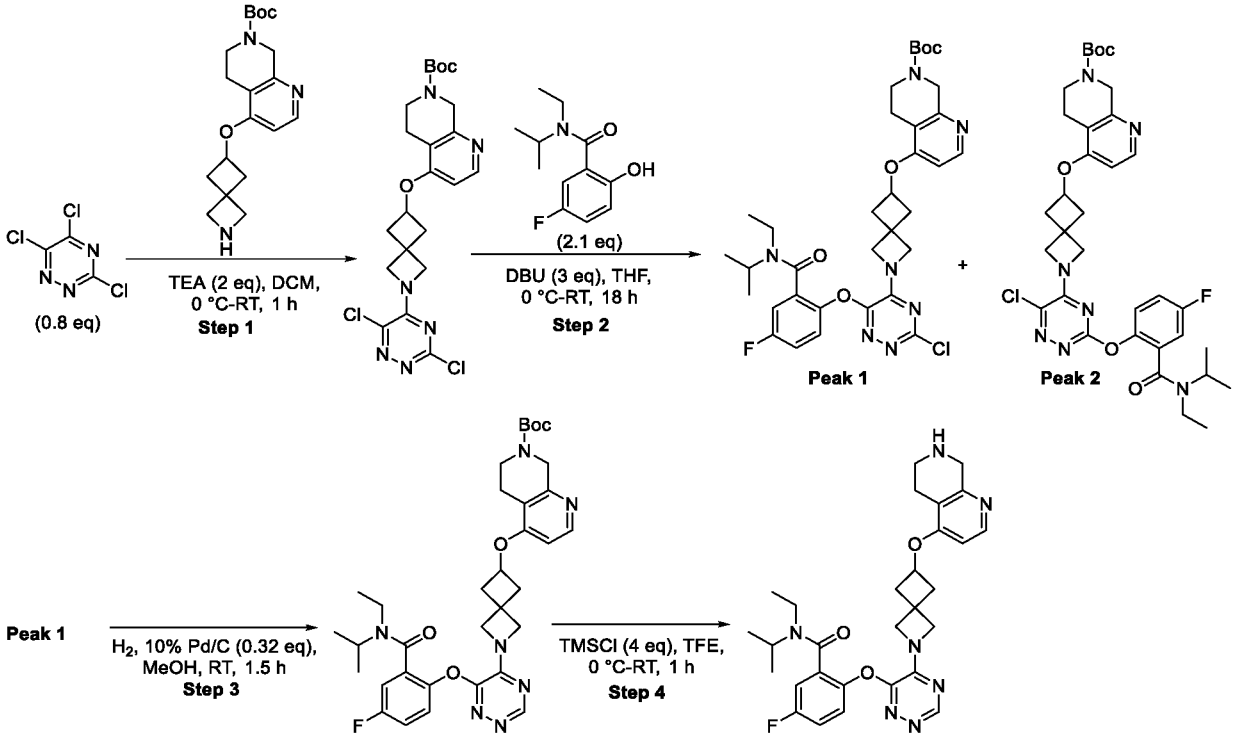
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride



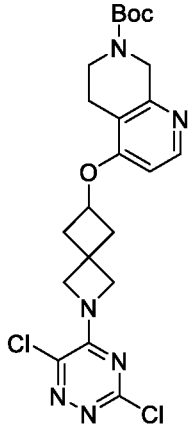
To a stirred solution of *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.12 g, 0.185 mmol) in 2,2,2-trifluoroethanol (6 mL), TMSCl (0.095 mL, 0.741 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by LCMS (method G). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was triturated with EtOAc (2 x 25 mL) and dried under reduced pressure to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-

yl)oxy)benzamide hydrochloride (0.106 g, 97% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (br s, 2H), 8.83 - 8.67 (m, 2H), 7.54 - 7.45 (m, 1H), 7.44 - 7.36 (m, 2H), 7.36 - 7.31 (m, 1H), 5.18 - 5.07 (m, 1H), 4.81 - 4.63 (m, 2H), 4.43 - 4.31 (m, 2H), 4.22 - 4.15 (m, 2H), 3.70 - 3.60 (m, 2H), 3.51 - 3.42 (m, 2H), 3.33 - 3.24 (m, 2H), 3.13 - 3.03 (m, 1H), 3.01 - 2.87 (m, 2H), 2.56 - 2.52 (m, 2H), 0.68 - 1.26 (m, 9H); LCMS (Method G): Rt = 2.09 min, m/z = 548.3 $[M+H]^+$; HPLC (Method A): Rt = 4.51 min, 99.03%.

Example 6. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 155)

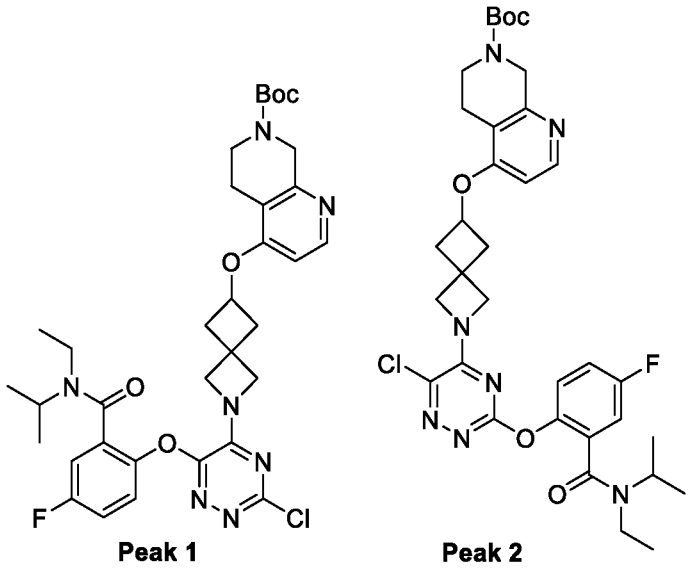


Step 1. tert-Butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



To a stirred solution of 3,5,6-trichloro-1,2,4-triazine (0.512 g, 2.78 mmol) in DCM (15 mL), TEA (0.976 mL, 6.95 mmol) was added at 0 °C, then *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (1.2 g, 3.47 mmol) was added in DCM (5 mL) under nitrogen atmosphere. The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (5% MeOH in DCM). The reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford a crude sticky liquid. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 4% MeOH in DCM) to obtain *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (830 mg, 44.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, J = 5.7 Hz, 1H), 6.73 (d, J = 5.8 Hz, 1H), 4.85 – 4.71 (m, 3H), 4.46 (br s, 2H), 4.29 – 4.12 (m, 2H), 3.58 (t, J = 5.7 Hz, 2H), 2.91 – 2.79 (m, 2H), 2.62 (t, J = 5.8 Hz, 2H), 2.39 – 2.28 (m, 2H), 1.43 (s, 9H); LCMS (Method B): Rt = 2.04 min, m/z = 493.0 $[M+H]^+$; 92.55%.

Step 2. tert-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate and tert-Butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



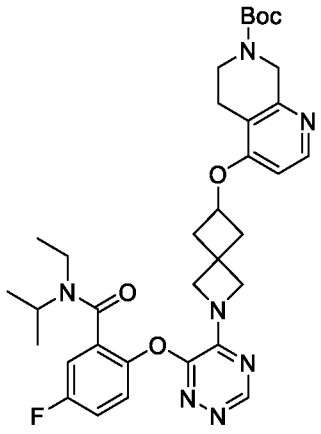
To a stirred solution of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (500 mg, 1.013 mmol) and *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (479 mg, 2.128 mmol) in

THF (7 mL), DBU (0.458 mL, 3.04 mmol) was added at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure, quenched with ice water (60 mL), and extracted with EtOAc (2 x 60 mL). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 75% -80% EtOAc in hexane) to obtain both regioisomers.

Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (250 mg, 33.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 – 8.20 (m, 1H), 7.49 – 7.42 (m, 1H), 7.41 – 7.32 (m, 2H), 6.74 (d, J = 5.7 Hz, 1H), 4.87 – 4.73 (m, 1H), 4.69 – 4.55 (m, 2H), 4.45 (br s, 2H), 4.30 – 4.19 (m, 2H), 3.69 – 3.47 (m, 3H), 3.46 – 3.39 (m, 1H), 3.20 – 3.01 (m, 1H), 2.91 – 2.77 (m, 2H), 2.65 – 2.58 (m, 2H), 2.40 – 2.28 (m, 2H), 1.46 – 1.40 (m, 9H), 1.17 – 0.76 (m, 9H). LCMS (Method D): Rt = 2.63 min, m/z = 682.4 $[M+H]^+$; 93.75%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (50 mg, 6.59% yield) as a solid. LCMS (Method D): Rt = 2.63 min, m/z = 682.4 $[M+H]^+$; 91.13%.

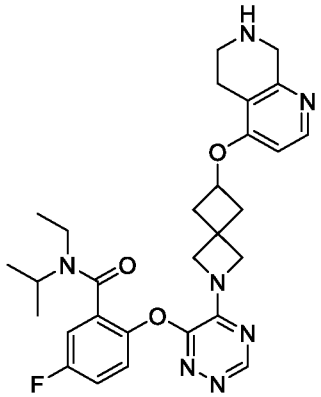
Step 3. tert-Butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



A solution of *tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (250 mg, 0.366 mmol) in dry MeOH (15 mL) was degassed

with nitrogen for 5 min. To this solution, 10% Pd-C (125 mg, 0.117 mmol) was added at RT. The reaction was stirred at RT for 1.5 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (100% EtOAc). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (200 mg, 73.8% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.45 (d, *J* = 5.9 Hz, 1H), 7.28 –7.25 (m, 1H), 7.20 – 7.13 (m, 1H), 7.10 – 7.02 (m, 1H), 6.86 – 6.79 (m, 1H), 5.02 (br s, 2H), 4.95 – 4.73 (m, 3H), 4.40 – 4.27 (m, 2H), 3.93 – 3.82 (m, 1H), 3.74 (t, *J* = 5.7 Hz, 2H), 3.57 – 3.44 (m, 1H), 3.28 – 3.10 (m, 1H), 3.04 – 2.93 (m, 2H), 2.81 (t, *J* = 5.3 Hz, 2H), 2.69 – 2.52 (m, 2H), 1.51 (s, 9H), 1.23 – 0.75 (m, 9H), 0.91 – 0.65 (m, 3H); LCMS (Method G): Rt = 2.11 min, m/z = 648.3 $[M+H]^+$; 87.61%. This material was used without further purification.

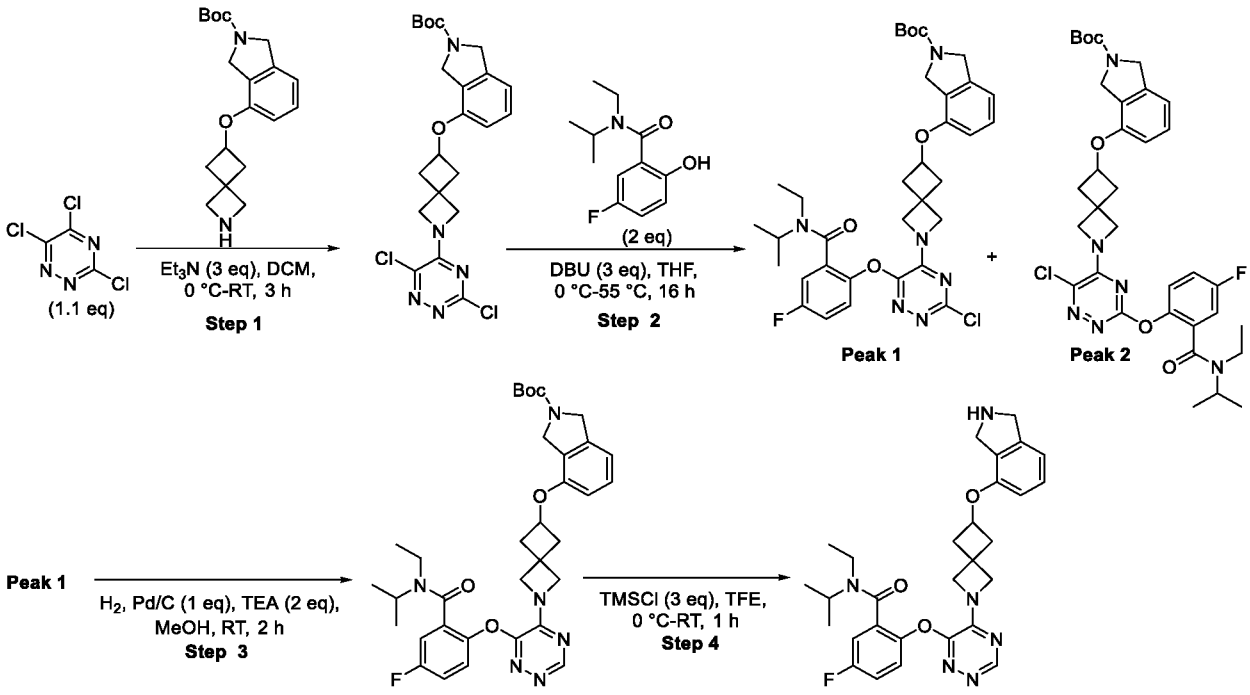
Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



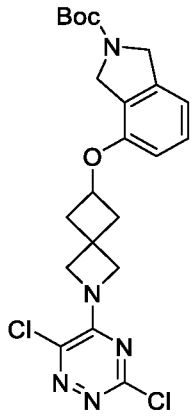
In a 25 mL round bottom flask, *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (200 mg, 0.309 mmol) was added in 2,2,2-trifluoroethanol (3 mL). To this solution, TMSCl (0.158 mL, 1.235 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to afford crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to afford an impure product (127 mg). The impure product was re-purified by

Prep HPLC (Method I). The pure fractions were concentrated under reduced pressure and lyophilized to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (21.11 mg, 12.48% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.48 – 7.32 (m, 3H), 6.66 (d, J = 5.6 Hz, 1H), 4.77 (quin, J = 6.6 Hz, 1H), 4.65 – 4.48 (m, 2H), 4.32 – 4.12 (m, 2H), 3.76 (s, 2H), 3.68 – 3.57 (m, 1H), 3.17 – 2.97 (m, 2H), 2.95 – 2.77 (m, 5H), 2.37 – 2.28 (m, 2H), 1.16 – 0.67 (m, 9H) two protons merged with solvent peaks; LCMS (Method G): Rt = 1.53 min, m/z = 548.5 $[M+H]^+$; HPLC (Method A): Rt = 4.57 min, 99.48%.

Example 7. *N*-Ethyl-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (Compound No. 7)

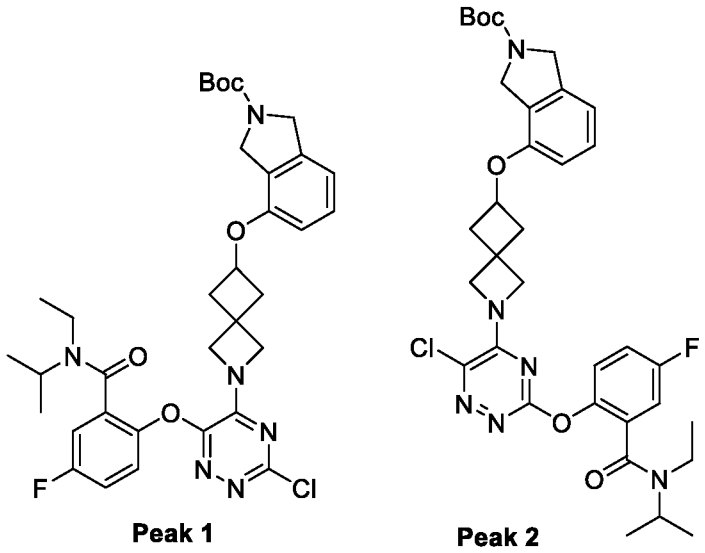


Step 1. tert-Butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



In a 100 mL two neck round bottom flask under nitrogen atmosphere, 3,5,6-trichloro-1,2,4-triazine (0.921 g, 4.99 mmol) was added in dichloromethane (20 mL). To this reaction mixture, Et_3N (1.898 mL, 13.62 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.5 g, 4.54 mmol) were added at 0 °C, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with water (20 mL) and extracted with DCM (2 x 30 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted in 50% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (1.1 g, 44.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (t, J = 7.8 Hz, 1H), 6.91 (dd, J = 5.2, 7.1 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 4.81 (s, 1H), 4.78 - 4.70 (m, 2H), 4.63 - 4.53 (m, 2H), 4.51 - 4.41 (m, 2H), 4.25 (br s, 1H), 4.18 (br s, 1H), 2.88 - 2.74 (m, 2H), 2.39 - 2.26 (m, 2H), 1.48 - 1.44 (m, 9H); LCMS (Method H): Rt = 2.45 min, m/z = 478.3 $[M+H]^+$, 87.89%.

Step 2. tert-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



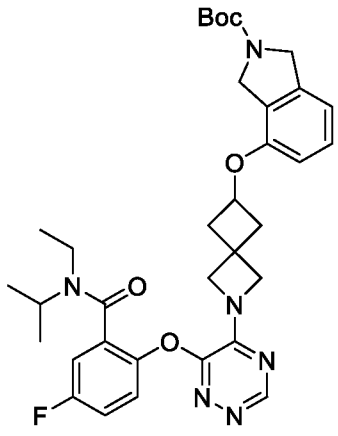
In a 50 mL single neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (600 mg, 1.254 mmol) was added in THF (10 mL). To this reaction mixture, *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (565 mg, 2.508 mmol) and DBU (0.567 mL, 3.76 mmol)

were added at 0 °C, and the reaction was stirred at 55 °C for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted in 50% EtOAc in hexane) to obtain both isomers.

Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (0.21 g, 25% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52 - 7.42 (m, 1H), 7.42 - 7.30 (m, 2H), 7.30 - 7.20 (m, 1H), 6.95 - 6.86 (m, 1H), 6.74 (d, J = 8.3 Hz, 1H), 4.80 - 4.62 (m, 2H), 4.62 - 4.53 (m, 3H), 4.51 - 4.36 (m, 2H), 4.32 - 4.17 (m, 2H), 3.69 - 3.54 (m, 1H), 3.20 - 3.00 (m, 2H), 2.89 - 2.72 (m, 2H), 2.39 - 2.24 (m, 2H), 1.50 - 1.39 (m, 9H), 1.26 - 0.91 (m, 9H); LCMS (Method D): Rt = 2.40 min, m/z = 667.1 $[M+H]^+$, 89.95%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (0.105 g, 12.5% yield). LCMS (Method D): Rt = 2.40 min, m/z = 667.1 $[M+H]^+$, 89.55%.

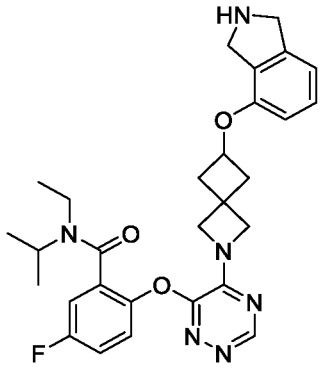
Step 3. tert-Butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



In a 25 mL single neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (0.2 g, 0.300 mmol) and Et_3N (0.061 g, 0.600 mmol) were added in methanol (10 mL). To this reaction mixture, Pd-C (0.032 g,

0.300 mmol) was added, and the reaction was stirred at RT for 2 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with methanol (15 mL). The filtrate was concentrated under reduced pressure to afford *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (0.115 g, 53.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.51 - 7.41 (m, 1H), 7.41 - 7.33 (m, 2H), 7.24 (t, J = 7.8 Hz, 1H), 6.96 - 6.86 (m, 1H), 6.75 (d, J = 8.1 Hz, 1H), 4.85 - 4.70 (m, 1H), 4.69 - 4.39 (m, 6H), 4.34 - 4.07 (m, 3H), 3.72 - 3.52 (m, 1H), 3.19 - 2.97 (m, 1H), 2.90 - 2.73 (m, 2H), 2.35 - 2.22 (m, 2H), 1.54 - 1.38 (m, 9H), 1.16 - 0.85 (m, 9H); LCMS (Method D): Rt = 2.22 min, m/z = 633.2 $[M+H]^+$, 87.81%.

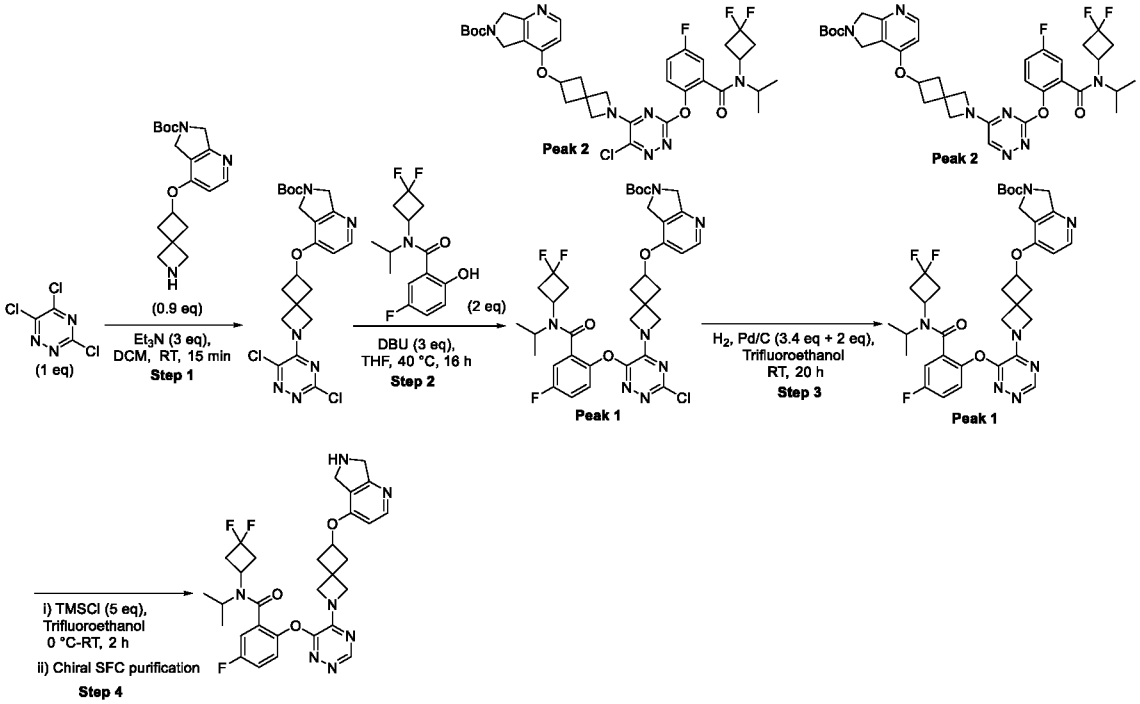
Step 4. N-Ethyl-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide



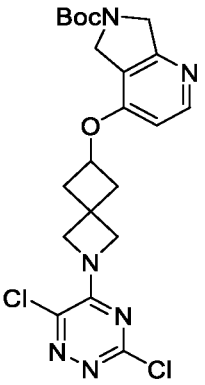
In a 25 mL round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (0.15 g, 0.237 mmol) was added in 2,2,2-trifluoro ethanol (5 mL). To this reaction mixture, TMSCl (0.091 mL, 0.711 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude *N*-ethyl-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropyl benzamide hydrochloride. The crude was purified by Prep HPLC (Method B) to obtain *N*-ethyl-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropyl benzamide (0.035 g, 27.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.51 - 7.41 (m, 1H), 7.41 - 7.31 (m, 2H), 7.13 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 4.81 - 4.41 (m, 4H), 4.36 - 4.11 (m, 2H), 4.09 - 3.94 (m, 3H), 3.69 - 3.57 (m, 1H), 3.48 - 3.39 (m,

1H), 3.19 - 2.94 (m, 2H), 2.87 - 2.72 (m, 2H), 2.32 - 2.21 (m, 2H), 1.19 - 0.63 (m, 9H); LCMS (Method D): Rt = 1.63 min, m/z = 533.1 $[M+H]^+$, 99.79%; HPLC (Method A): Rt = 4.81 min, 99.87%.

Example 8. *N*-(3,3-Difluorocyclobutyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 283)



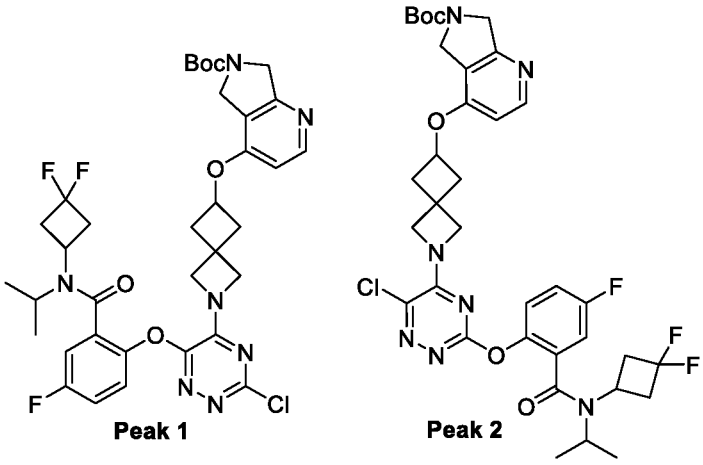
Step 1. tert-Butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



In a dried, 50 mL two-neck round bottom flask under nitrogen atmosphere, Et_3N (0.794 mL, 5.69 mmol) was added to a stirred solution of 3,5,6-trichloro-1,2,4-triazine (0.350 g, 1.898 mmol) in DCM (10 mL) at 0 °C. To this solution, *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (0.566 g, 1.708 mmol) in DCM (2 mL) was added at the same temperature. The reaction was stirred at RT for 15 min. The

progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 2% MeOH in DCM) to obtain *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (0.340 g, 37.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, J = 5.8 Hz, 1H), 6.82 (d, J = 5.8 Hz, 1H), 4.91 - 4.70 (m, 3H), 4.58 - 4.44 (m, 4H), 4.31 - 4.12 (m, 2H), 2.94 - 2.78 (m, 2H), 2.44 - 2.31 (m, 2H), 1.47 (s, 9H); LCMS (Method G): Rt = 2.21 min, m/z = 479.2 $[M+H]^+$, 99.81%.

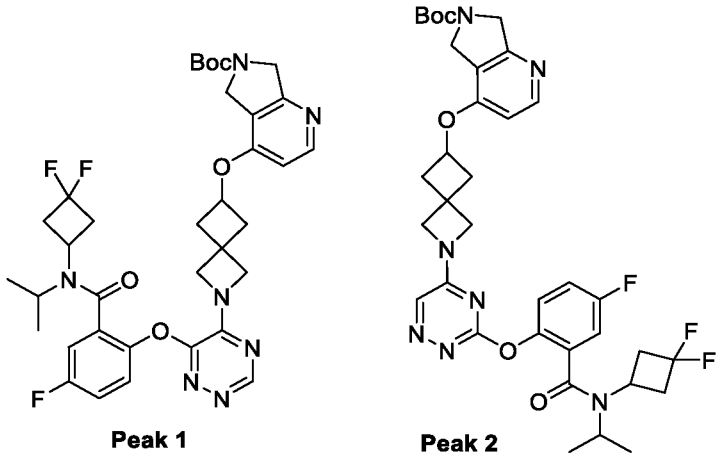
Step 2. tert-Butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



In a dried, 50 mL two-neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (340 mg, 0.709 mmol) was added in THF (10 mL). To this solution, *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (408 mg, 1.419 mmol) and DBU (0.318 mL, 2.128 mmol) were added at 0 °C. The reaction was stirred at 40 °C for 16 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with water (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude

product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 90% EtOAc in hexane) to afford a mixture of *tert*-butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer (~6:4) (350 mg, 61.8% yield)) as a solid. LCMS (Method G): Rt = 2.39 min, m/z = 730.6 $[M+H]^+$, 91.46%. This mixture of regioisomers was used without further purification.

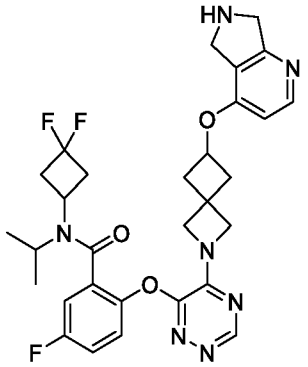
Step 3. tert-Butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and tert-butyl 4-((2-(3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



In a dried, 50 mL round bottom flask under nitrogen atmosphere, a mixture of *tert*-butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer (~6:4) (320 mg, 0.438 mmol) was added in 2,2,2 trifluoroethanol (10 mL). To this solution, Pd-C (160 mg, 1.503 mmol) was added, and the reaction was stirred at RT for 4 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). The starting material was not consumed completely. Therefore, another lot of Pd-C (93 mg, 0.876 mmol) was added, and the reaction was stirred at RT under a hydrogen atmosphere (balloon pressure) for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude mixture of *tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate

and the other regioisomer (300 mg, 83% yield) as a viscous liquid. LCMS (Method D): Rt = 2.14 min, m/z= 696.2 $[M+H]^+$, 84.28%. This mixture of regioisomers was used without further purification.

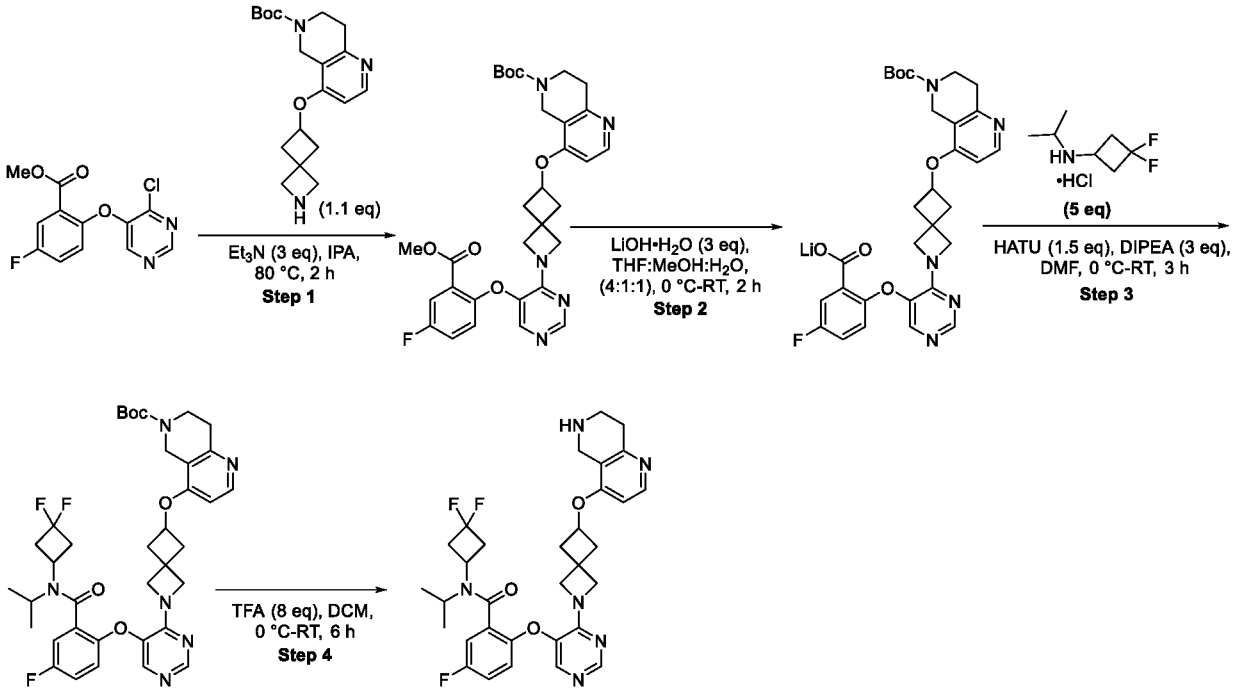
Step 4. N-(3,3-Difluorocyclobutyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide



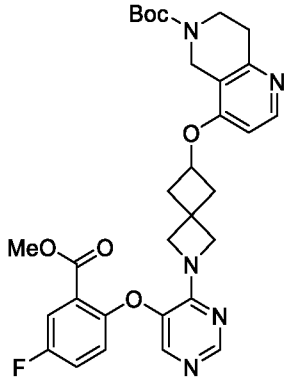
In a dried, 50 mL round bottom flask under nitrogen atmosphere, a mixture of *tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer (300 mg, 0.431 mmol) was dissolved in 2,2,2 trifluoroethanol (5 mL). To this solution, TMSCl (0.276 mL, 2.156 mmol) was added at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc (2 x 10 mL). The organic layer was decanted, and the resulting solid was dried under reduced pressure to afford crude *N*-(3,3-difluorocyclobutyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide hydrochloride. To this crude material, sodium bicarbonate solution (15 mL) was added, and the mixture was extracted with 10% MeOH in DCM (3 x 15 mL). The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound. The crude product was purified using achiral Prep SFC (Method B), then by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), to obtain *N*-(3,3-difluorocyclobutyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (39.79 mg, 0.065 mmol, 17.52% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H), 7.53 - 7.23 (m, 3H), 6.78 - 6.63 (m, 1H), 4.83 (quin, J = 6.6 Hz, 1H), 4.71 - 4.45 (m, 2H), 4.34 - 4.13 (m, 2H), 4.12 - 3.94 (m, 4H), 3.93 - 3.78 (m, 1H),3.77 – 3.41 (m, 3 H), 2.91 - 2.62 (m, 5H), 2.43 - 2.21

(m, 2H), 1.53 – 0.53 (m, 6H); LCMS (Method G): Rt = 1.70 min, m/z= 596.5 $[M+H]^+$; HPLC (Method D): Rt = 3.17 min, 97.54%.

Example 9. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 131)



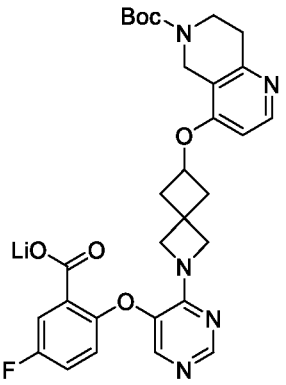
Step 1. tert-Butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 100 mL single neck round bottom flask under nitrogen atmosphere, methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (1.6 g, 5.66 mmol) was added in 2-propanol (15 mL). To this solution, Et_3N (2.367 mL, 16.98 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (2.151 g, 6.23 mmol) was added at 0 °C. The reaction was stirred at 80 °C for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced

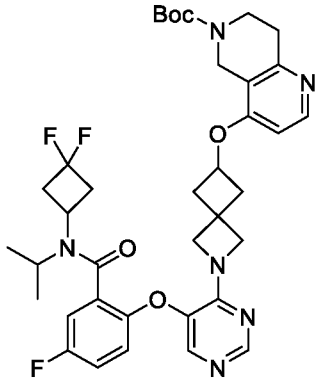
pressure to obtain the crude product. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.32 g, 33.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H), 7.70 - 7.65 (m, 2H), 7.52 - 7.45 (m, 1H), 7.11 (dd, J = 4.5, 9.2 Hz, 1H), 6.75 (d, J = 5.7 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.44 - 4.16 (m, 6H), 3.85 - 3.77 (m, 3H), 3.61 (t, J = 5.8 Hz, 2H), 2.90 - 2.72 (m, 4H), 2.38 - 2.20 (m, 2H), 1.51 - 1.38 (m, 9H); LCMS (Method B): Rt = 1.87 min, m/z = 592.2 $[M+H]^+$, 85.31%.

Step 2. 2-((4-(6-((6-(tert-Butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid



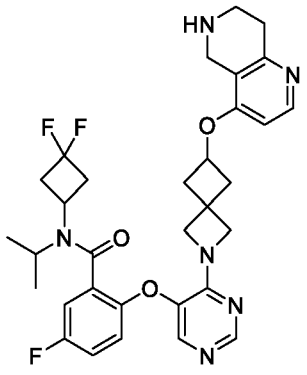
To a stirred solution of *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (400 mg, 0.676 mmol) in THF:MeOH (4:1, 5 mL), a solution of $LiOH.H_2O$ (85 mg, 2.028 mmol) in water (1 mL) was added at 0 °C. The reaction was stirred for 2 h at RT. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude compound. The crude compound was co-distilled with toluene (3 x 15 mL) to afford lithium 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate as a solid (380 mg, 95.9% yield). LCMS (Method B): Rt = 1.72 min, m/z = 578.3 $[M+H]^+$, 89.81%. This material was used without further purification.

Step 3. tert-Butyl 4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



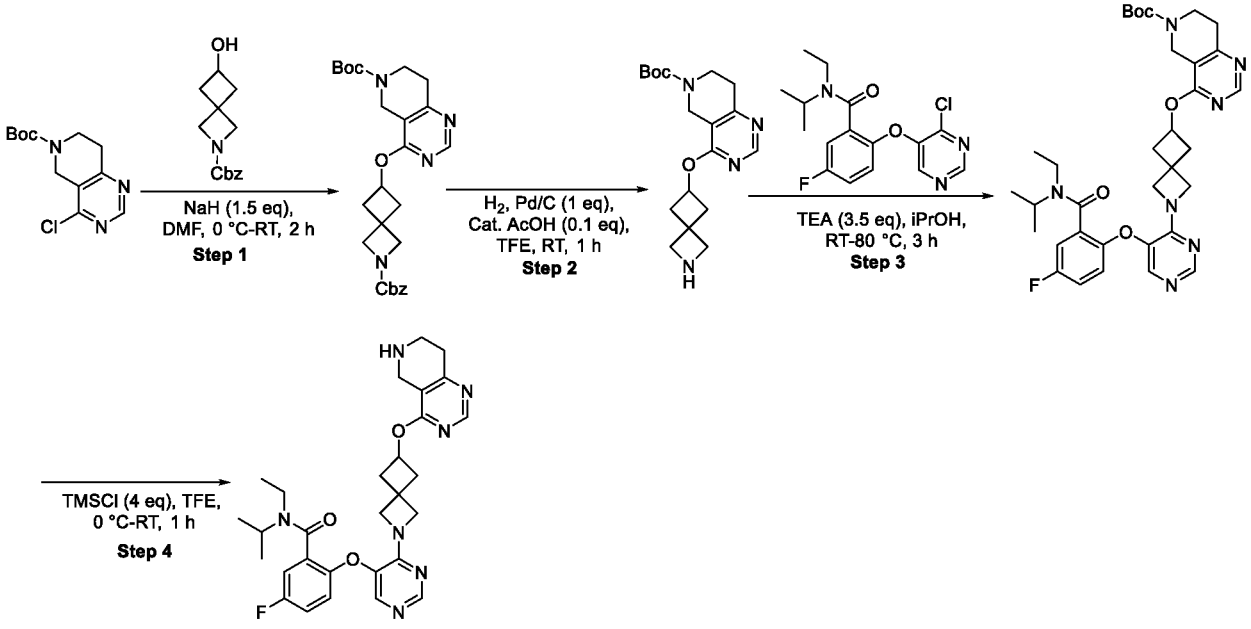
To a stirred solution of lithium 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate (390 mg, 0.668 mmol) in DMF (6 mL), HATU (381 mg, 1.002 mmol), DIPEA (0.350 mL, 2.005 mmol) and 3,3-difluoro-*N*-isopropylcyclobutan-1-amine (499 mg, 3.34 mmol) were added at 0 °C. The reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with water (20 mL) and extracted with 10% MeOH in DCM (3 x 25 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 9% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (200 mg, 38.7% yield). LCMS (Method B): Rt = 2.093 min, m/z = 709.2 $[M+H]^+$,91.71%.

Step 4. N-(3,3-Difluorocyclobutyl)-5-Fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

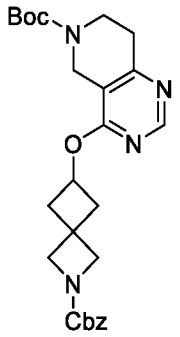


To a stirred solution of *tert*-butyl 4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (170 mg, 0.24 mmol) in DCM (5 mL), trifluoroacetic acid (0.148 mL, 1.919 mmol) was added at 0 °C. The reaction was stirred at RT for 6 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (110 mg, 74.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, *J* = 2.9, 8.1 Hz, 1H), 7.27 (dt, *J* = 3.0, 8.6 Hz, 1H), 7.05 (dd, *J* = 4.3, 9.0 Hz, 1H), 6.63 (d, *J* = 5.6 Hz, 1H), 4.72 (quin, *J* = 6.6 Hz, 1H), 4.35 - 4.04 (m, 4H), 3.98 - 3.83 (m, 1H), 3.79 - 3.71 (m, 1H), 3.69 (s, 2H), 3.62 - 3.47 (m, 1H), 2.94 (t, *J* = 5.8 Hz, 2H), 2.84 - 2.62 (m, 7H), 2.30 - 2.18 (m, 2H), 1.51 - 1.21 (m, 1H), 1.15 - 0.94 (m, 6H); LCMS (Method B): Rt = 1.45 min, m/z = 609.6 $[M+H]^+$; HPLC (Method A): Rt = 5.39 min, 97.94%.

Example 10. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 68)

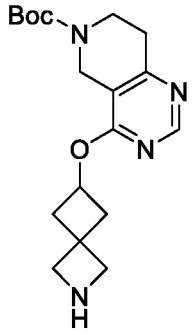


Step 1. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



In 100 mL two neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-chloro-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (1 g, 3.71 mmol) and benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (0.917 g, 3.71 mmol) were added in DMF (10 mL). To this stirred solution, NaH (0.222 g, 5.56 mmol) was added at 0 °C, and the reaction was warmed to RT over 2 h. The reaction progress was monitored by TLC (70% EtOAc in hexane). The reaction was diluted with cold water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude product. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 94% EtOAc in hexane) to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (450 mg, 23.35% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (s, 1H), 7.41 – 7.23 (m, 5H), 5.17 (quin, J = 6.9 Hz, 1H), 5.02 (s, 2H), 4.33 (s, 2H), 4.06 – 3.86 (m, 4H), 3.63 (t, J = 5.7 Hz, 2H), 2.83 – 2.71 (m, 4H), 2.38 – 2.22 (m, 2H), 1.43 (s, 9H); LCMS (Method B): Rt = 2.81 min, m/z = 481.4 $[M+H]^+$; 92.46%.

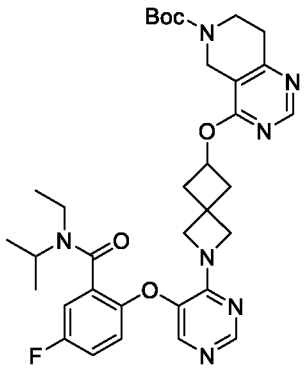
Step 2. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



In a 100 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-

6(5H)-carboxylate (450 mg, 0.936 mmol) was added in 2,2,2-trifluoroethanol (10 mL). To this stirred solution, Pd-C (199 mg, 0.936 mmol) and AcOH (5.36 µL, 0.094 mmol) were added at RT. The reaction was stirred at RT for 1 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (5% MeOH in DCM). The reaction was purged with nitrogen gas for 5 min, filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (305 mg, 86% yield) as a liquid. LCMS (Method D): Rt = 1.39 min, m/z = 347.2 $[M+H]^+$; 91.50%. This material was used without further purification.

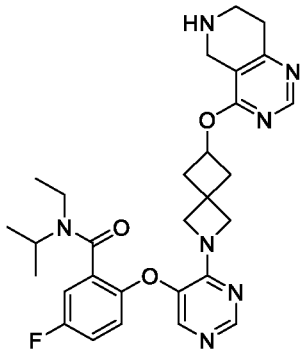
Step 3. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



In 100 mL round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (305 mg, 0.880 mmol) was added in IPA (10 mL). To this stirred solution, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (381 mg, 0.880 mmol) and TEA (0.430 mL, 3.08 mmol) were added at RT. The reaction was stirred at 80 °C for 3 h. The reaction progress was monitored by TLC (5% MeOH in DCM). The reaction was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford a crude liquid. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (450 mg, 70.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.32 - 8.24 (m, 1H), 7.79 - 7.63 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 6.98 (m, 1H), 5.22 - 5.14 (m, 1H), 4.34 (s, 2H), 4.30 - 4.08 (m, 4H), 3.82 - 3.69 (m, 1H), 3.64 (t, J = 5.6 Hz, 2H), 3.47 - 3.36 (m, 1H),

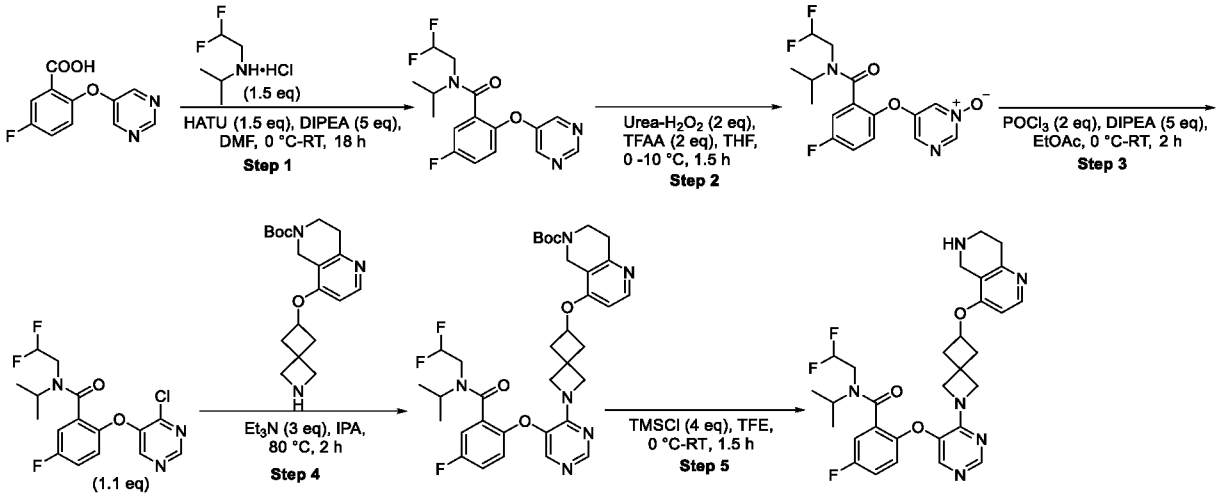
3.29 - 3.10 (m, 1H), 2.82 - 2.69 (m, 4H), 2.38 - 2.25 (m, 2H), 1.43 (s, 9H), 1.23 - 0.97 (m, 9H); LCMS (Method B): Rt = 2.32 min, m/z = 648.3 $[M+H]^+$; 88.97%.

Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

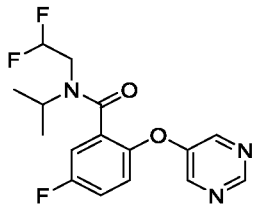


In 100 mL round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (450 mg, 0.695 mmol) was added in 2,2,2-trifluoroethanol (10 mL). To this stirred solution, TMSCl (0.355 ml, 2.78 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (400 mg). The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain impure product (135 mg, LCMS-89%) as a solid. This material was re-purified by Prep HPLC (Method A). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (38.93 mg, 10.15% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (s, 1H), 8.33 – 8.25 (m, 1H), 7.79 – 7.66 (m, 1H), 7.34 – 7.21 (m, 2H), 7.09 – 6.97 (m, 1H), 5.18 – 5.09 (m, 1H), 4.47 – 4.08 (m, 4H), 3.86 – 3.69 (m, 1H), 3.65 (s, 2H), 3.48 – 3.37 (m, 1H), 3.28 – 3.11 (m, 2H), 2.96 (t, J = 5.7 Hz, 2H), 2.77 – 2.69 (m, 2H), 2.63 (t, J = 5.5 Hz, 2H), 2.32 – 2.25 (m, 2H), 1.23 – 0.99 (m, 9H); LCMS (Method B): Rt = 1.56 min, m/z = 548.4 $[M+H]^+$; HPLC (Method A): Rt = 4.73 min, 99.17%.

Example 11. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 58)

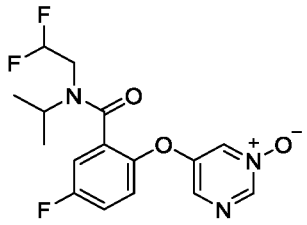


Step 1. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)benzamide



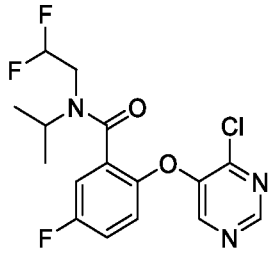
In a 250 mL two neck round bottom flask under a nitrogen atmosphere, 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (2.9 g, 12.38 mmol) was dissolved in DMF (30 mL). To this solution, *N*-(2,2-difluoroethyl)propan-2-amine hydrochloride (2.96 g, 18.57 mmol), DIPEA (10.79 mL, 61.9 mmol) and HATU (7.06 g, 18.57 mmol) were added at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 18 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (the product eluted at 25-30% EtOAc in hexane) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (4.2 g, 97 % yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.55 (s, 2H), 7.46 – 7.27 (m, 3H), 6.07 (tt, J = 4.4, 56.9 Hz, 1H), 3.88-3.81 (m, 1H), 3.76 – 3.45 (m, 2H), 1.09 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); LCMS: (Method D): Rt = 1.69 min, m/z = 340.0 $[M+H]^+$, 96.91%.

Step 2. 5-(2-((2,2-Difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide



In a 100 mL two neck round bottom flask under a nitrogen atmosphere, *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)benzamide (2.2 g, 6.48 mmol) was dissolved in THF (25 mL) at 0 °C. To this solution, urea hydrogen peroxide (1.220 g, 12.97 mmol) and TFAA (1.832 mL, 12.97 mmol) were added slowly. The reaction was stirred at 0 °C-10 °C for 1.5 h. The progress of the reaction was monitored by TLC (70% EtOAc in hexane). After completion, the reaction was quenched with saturated sodium bicarbonate solution (30 mL; the temperature was maintained at 0 - 10 °C) and extracted with DCM (3 x 100 mL). The combined organic layer was washed with 1M $Na_2S_2O_3$ solution (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain 5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (2.5 g, 99% yield) as a semi-solid. LCMS (Method D): Rt = 1.48 min, m/z = 356.2 $[M+H]^+$, 91.14%.

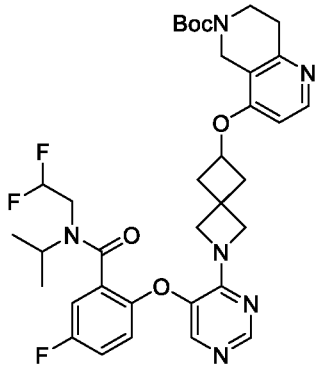
Step 3. 2-((4-Chloropyrimidin-5-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



In a 100 mL two neck round bottom flask under nitrogen atmosphere, 5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidine 1-oxide (2.5 g, 7.04 mmol) was dissolved in EtOAc (25 mL). To this solution, DIPEA (6.14 mL, 35.2 mmol) and $POCl_3$ (1.312 mL, 14.07 mmol) were added at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography by using EtOAc in hexane (product eluted at 25-30% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (1.3 g, 47.9% yield) as a semi-solid. ^1H NMR (400 MHz, DMSO-d_6); δ 8.83 (s, 1H), 8.41 (s, 1H), 7.46 (dd, J = 3.2, 7.6 Hz, 1H), 7.38 (spt, J

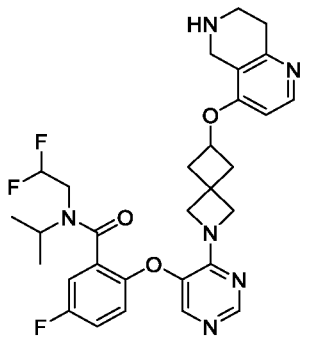
= 2.6 Hz, 2H), 6.24 – 5.94 (m, 1H), 3.88 – 3.70 (m, 1H), 3.68 (s, 2H), 1.09 (d, *J* = 6.5 Hz, 6H); LCMS (Method D): Rt = 1.87 min, m/z = 374.0 $[M+H]^+$, 96.89%.

Step 4. tert-Butyl 4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



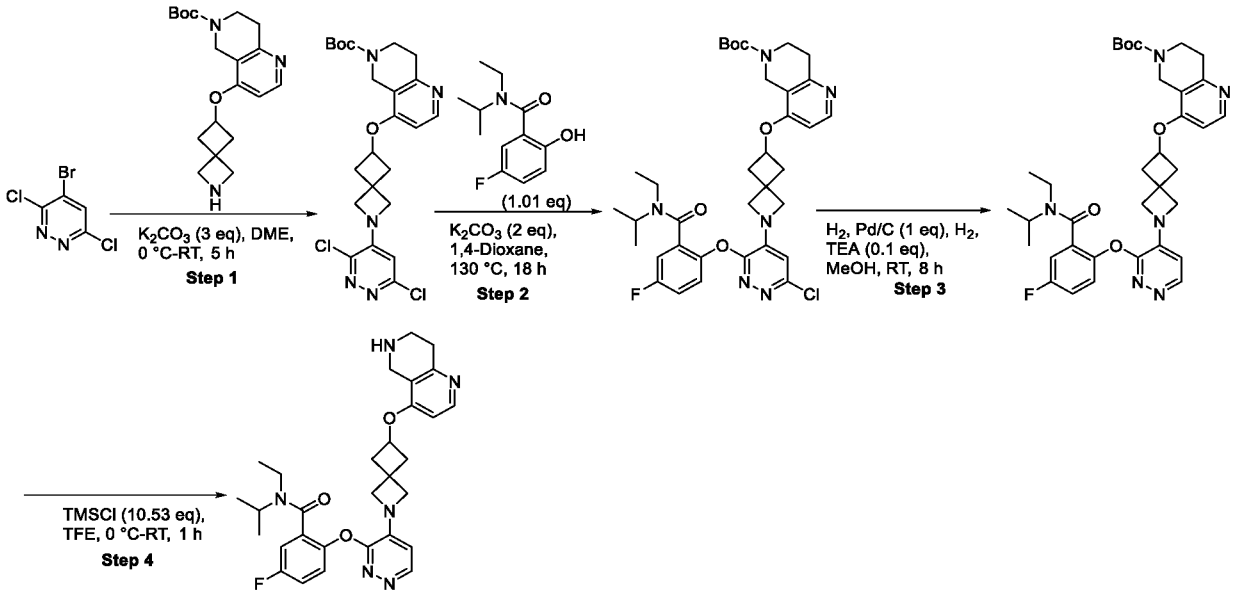
To a stirred solution of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.13 g, 0.376 mmol) in IPA (5 mL), TEA (0.158 mL, 1.129 mmol) was added at RT under nitrogen atmosphere. To this reaction mixture, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (0.155 g, 0.414 mmol) was added, and the reaction was stirred at 80 °C for 2 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.15 g, 50.4% yield) as a semi-solid. LCMS (Method D): Rt = 2.09 min, m/z = 683.2 $[M+H]^+$, 86.33%.

Step 5. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

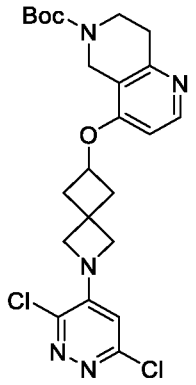


To a stirred solution of *tert*-butyl 4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (150 mg, 0.220 mmol) in 2,2,2-trifluororethanol (5 mL), TMSCl (0.11 mL 0.879 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by Prep HPLC (Method N) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (39.07 mg, 30.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.29 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.38 – 7.32 (m, 1H), 7.32 – 7.25 (m, 1H), 7.06 – 6.97 (m, 1H), 6.64 (d, J = 5.7 Hz, 1H), 6.39 – 6.03 (m, 1H), 4.82 – 4.62 (m, 1H), 4.27 – 4.04 (m, 4H), 3.93 – 3.58 (m, 3H), 2.95 (t, J = 5.8 Hz, 2H), 2.85 – 2.74 (m, 2H), 2.71 – 2.64 (m, 3H), 2.36 – 2.32 (m, 1H), 2.27 – 2.19 (m, 2H), 1.14 – 1.04 (m, 6H), -NH proton not observed; LCMS (Method B): Rt = 1.40 min, m/z = 583.0 $[M+H]^+$; HPLC (Method A): Rt = 4.84 min, 98.82%; Chiral SFC (Method E): Rt = 3.45 min, 100%.

Example 12. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)benzamide (Compound No. 213)

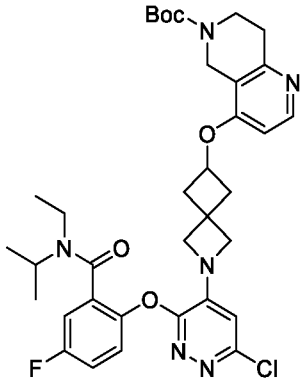


Step 1. tert-Butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 250 mL round bottom flask under a nitrogen atmosphere, 4-bromo-3,6-dichloropyridazine (3 g, 13.17 mmol) was added in DME (85 mL). To this stirred solution, K_2CO_3 (5.46 g, 39.5 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (4.55 g, 13.17 mmol) were added at 0 °C. The reaction was stirred at RT for 5 h. The reaction was monitored by TLC (70% EtOAc in hexane). The reaction was quenched with water (25 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude product. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain *tert*-butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (6.4 g, 89% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, J = 5.6 Hz, 1H), 6.76 (d, J = 5.6 Hz, 1H), 6.71 (s, 1H), 4.81 (quin, J = 6.5 Hz, 1H), 4.49 – 4.24 (m, 6H), 3.63 (t, J = 5.9 Hz, 2H), 2.91 – 2.65 (m, 4H), 2.38 – 2.30 (m, 2H), 1.44 (s, 9H); LCMS (Method D): Rt = 2.10 min, m/z = 492.1 $[M+H]^+$; 90.87%.

Step 2. tert-Butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

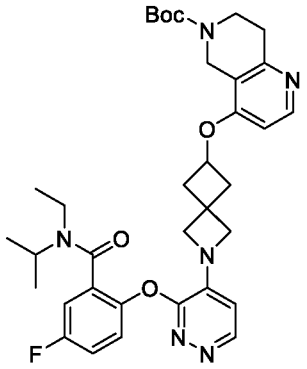


Step 2 was performed following the same procedure in two batches, a 5 g batch and a 1 g batch.

To a stirred solution of *tert*-butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (5.5 g, 11.17 mmol) in 1,4-dioxane (450 mL), *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (2.54 g, 11.28 mmol) and potassium carbonate (3.09 g, 22.34 mmol) were added at RT under nitrogen atmosphere. The reaction was stirred at 130 °C for 18 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude product. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM) to obtain *tert*-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (4 g, 31% yield). LCMS: (Method D): Rt = 2.23 min, m/z = 681.1 $[M+H]^+$; 58.97%.

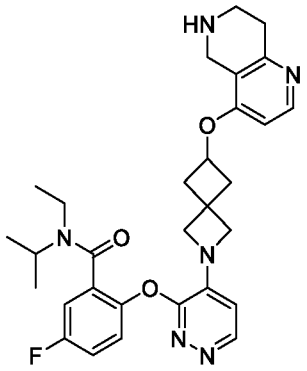
The crude product from both batches (4 g and 1 g) were combined and purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (2.96 g, 58.4% combined yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 5.6 Hz, 1H), 7.41 – 7.29 (m, 3H), 6.76 (d, J = 5.8 Hz, 1H), 6.56 (s, 1H), 4.81 (quin, J = 6.5 Hz, 1H), 4.38 (s, 2H), 4.34 – 4.19 (m, 3H), 3.68 – 3.58 (m, 3H), 3.45 – 3.36 (m, 1H), 3.15 – 3.04 (m, 1H), 2.90 – 2.76 (m, 4H), 2.38 – 2.25 (m, 2H), 1.46 – 1.40 (m, 9H), 1.15 – 0.67 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 2.15 min, m/z = 681.5 $[M+H]^+$; 98.65%.

Step 3. tert-Butyl 4-((2-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



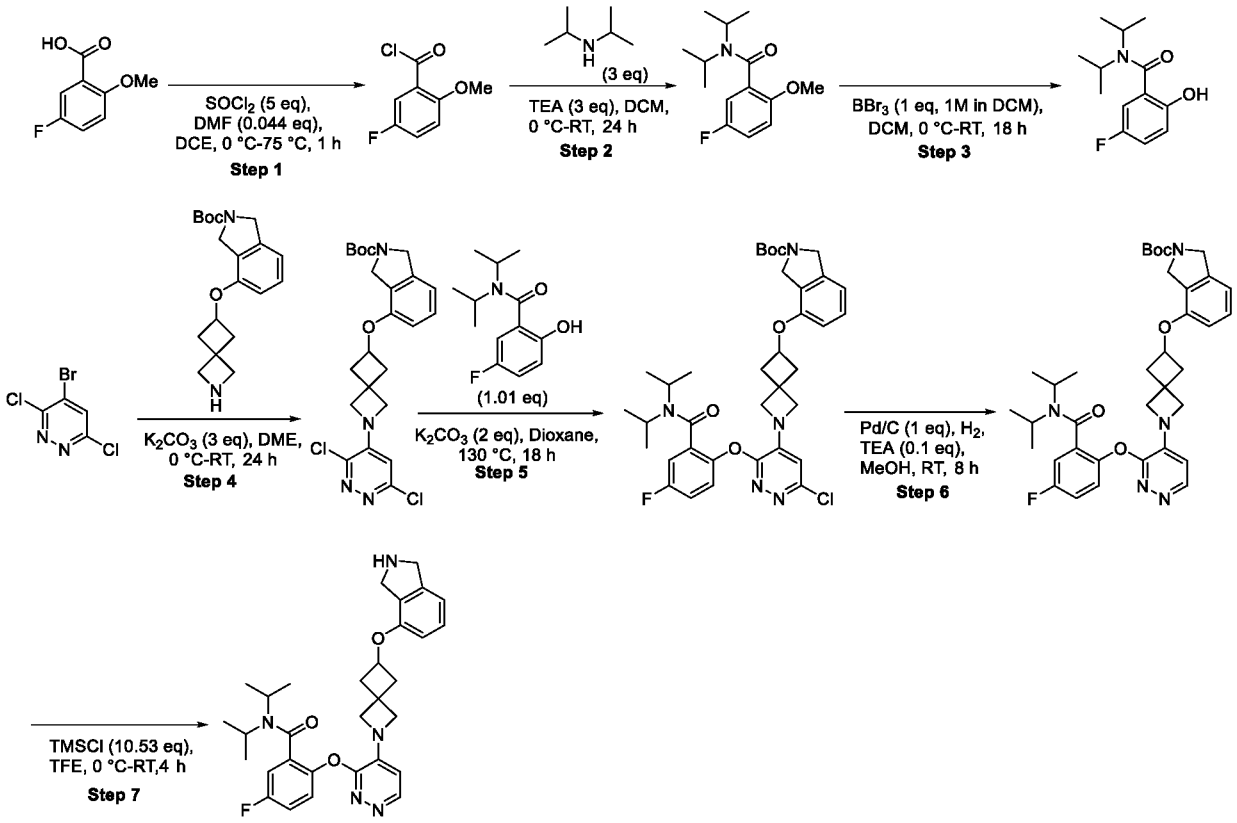
To a stirred solution of *tert*-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (2.96 g, 4.35 mmol) in MeOH (84 mL), TEA (0.061 mL, 0.435 mmol) and Pd-C (0.925 g, 4.35 mmol) were added at RT. The reaction was stirred for 8 h under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 100 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 15% MeOH in DCM) to obtain *tert*-butyl 4-((2-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.03 g, 36.65% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, J = 5.4 Hz, 1H), 8.24 (d, J = 5.7, Hz, 1H), 7.35 – 7.28 (m, 3H), 6.76 (d, J = 5.7 Hz, 1H), 6.45 (d, J = 5.4, Hz, 1H), 4.81 (quin, J = 6.6 Hz, 1H), 4.38 (s, 2H), 4.27 – 4.11 (m, 4H), 3.72 – 3.59 (m, 3H), 3.44 – 3.36 (m, 1H), 3.13 – 3.03 (m, 1H), 2.89 – 2.76 (m, 4H), 2.37 – 2.26 (m, 2H), 1.43 (s, 9H), 1.14 – 0.60 (m, 9H); LCMS (Method B): Rt = 1.43 min, m/z = 647.2 $[M+H]^+$; 91.49%.

Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)benzamide

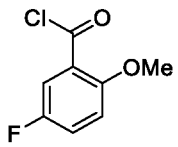


To a stirred solution of *tert*-butyl 4-((2-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.5 g, 0.773 mmol) in TFE (5 mL), TMSCl (1.040 mL, 8.14 mmol) was added at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was triturated with EtOAc (2 x 10 mL), and the organic layer was decanted. The residue was dried under a vacuum to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)benzamide hydrochloride (300 mg). The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were concentrated under reduced pressure to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)benzamide (0.42 g, 97% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.37 – 7.26 (m, 3H), 6.66 (d, J = 5.7 Hz, 1H), 6.45 (d, J = 5.5, Hz, 1H), 4.76 (quin, J = 6.6 Hz, 1H), 4.34 – 4.10 (m, 4H), 3.71 (s, 2H), 3.70 – 3.64 (m, 1H), 3.42 – 3.37 (m, 1H), 3.13 – 3.03 (m, 1H), 2.95 (t, J = 5.9 Hz, 2H), 2.80 – 2.79 (m, 2H), 2.72 – 2.65 (m, 2H), 2.33 – 2.20 (s, 2H), 1.17 – 0.61 (m, 9H) one proton merged in solvent peak; LCMS (Method G): Rt = 1.49 min, m/z = 547.5 $[M+H]^+$; HPLC (Method A): Rt = 4.51 min, 99.88%.

Example 13. 5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*,*N*-diisopropylbenzamide (Compound No. 19)

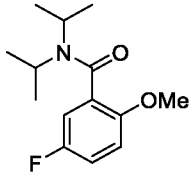


Step 1. 5-Fluoro-2-methoxybenzoyl chloride



To a stirred solution of 5-fluoro-2-methoxybenzoic acid (12.5 g, 73.5 mmol) in DCE (150 mL), thionyl chloride (26.8 mL, 367 mmol) was added slowly, followed by a catalytic amount of DMF (0.251 mL, 3.23 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 10 min and then at 75 °C for 1 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to afford crude 5-fluoro-2-methoxybenzoyl chloride (13 g, 94% yield). This material was used without further purification.

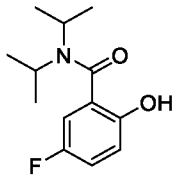
Step 2. 5-Fluoro-N, N-diisopropyl-2-methoxybenzamide



Step 2 was performed following the same procedure in three batches, 15.2 g, 15.3 g, and 50 g.

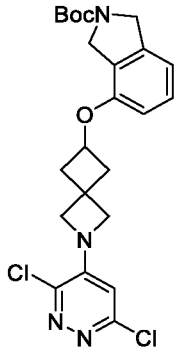
To a dried, 500 mL two neck round bottom flask under nitrogen atmosphere, 5-fluoro-2-methoxybenzoyl chloride (15.3 g, 81 mmol) was added in DCM (100 mL). To this solution, TEA (33.9 mL, 243 mmol) and diisopropylamine (34.4 mL, 243 mmol) were added at 0 °C. The reaction was stirred at RT for 24 h and monitored by TLC (30% EtOAc in hexane). After completion, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude (23 g) product. The crude products from three batches (19.1 g, 23 g, and 50 g, respectively) were combined and purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted in 12% EtOAc in hexane) to afford 5-fluoro-*N*,*N*-diisopropyl-2-methoxybenzamide (78 g, 72.13% combined yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (ddd, *J* = 3.1, 8.0, 9.0 Hz, 1H), 6.90 (dd, *J* = 3.1, 8.0 Hz, 1H), 6.83 (dd, *J* =4.1, 9.0 Hz, 1H), 3.81 (s, 3H), 3.67 (spt, *J* = 6.7 Hz, 1H), 3.51 (spt, *J* = 6.8 Hz, 1H), 1.56 (dd, *J* = 5.5, 6.8 Hz, 6H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H); LCMS (Method D): Rt = 1.88 min, m/z = 254.2 $[M+H]^+$; 97.33%.

Step 3. 5-Fluoro-2-hydroxy-N,N-diisopropylbenzamide



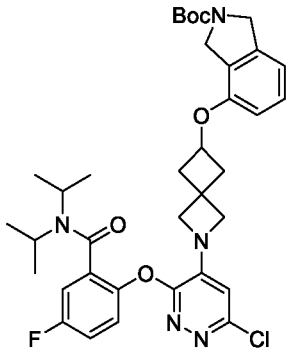
To a stirred solution of 5-fluoro-*N*,*N*-diisopropyl-2-methoxybenzamide (5 g, 19.74 mmol) in DCM (5 mL), BBr_3 (19.74 mL, 19.74 mmol, 1M in DCM) was added at 0 °C. The reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). The reaction was quenched with water (20 mL) and extracted with DCM (2 x 50 mL). The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide (4.5 g, 79% Yield). LCMS (Method D): Rt = 1.68 min, m/z = 240.1 $[M+H]^+$; 79.60%. This material was used without further purification.

Step 4. tert-Butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



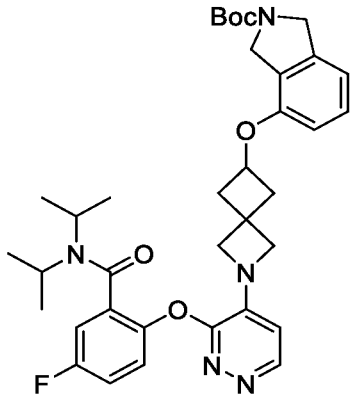
In a 50 mL round bottom flask under a nitrogen atmosphere, 4-bromo-3,6-dichloropyridazine (350 mg, 1.536 mmol) was added in DME (10 mL). To this reaction mixture, K_2CO_3 (637 mg, 4.61 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (508 mg, 1.536 mmol) were added at 0 °C, and the reaction was stirred at RT for 24 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was diluted with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 40% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (460 mg, 60.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (t, J = 7.9 Hz, 1H), 6.93 – 6.85 (m, 1H), 6.77 – 6.70 (m, 2H), 4.73 (quin, J = 6.7 Hz, 1H), 4.63 – 4.44 (m, 4H), 4.43 – 4.26 (m, 4H), 2.85 – 2.76 (m, 2H), 2.36 – 2.26 (m, 2H), 1.48 – 1.44 (s, 9H); LCMS (Method H): Rt = 2.58 min, m/z = 477.2 $[M+H]^+$; 97.11%.

Step 5. tert-Butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



In a 50 mL two neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(3,6-dichloropyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (360 mg, 0.754 mmol) was added in 1,4-dioxane (30 mL). To this solution, 5-fluoro-2-hydroxy-*N*, *N*-diisopropylbenzamide (182 mg, 0.762 mmol), and K_2CO_3 (208 mg, 1.508 mmol) were added, then the reaction mixture was purged with nitrogen for 5 min. The reaction was stirred at 130 °C for 18 h and monitored by TLC (50% EtOAc in hexane). The reaction was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 40% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (450 mg, 88% yield) as off white solid. LCMS (Method H): Rt = 2.62 min, m/z = 680.2 $[M+H]^+$; 80.55%.

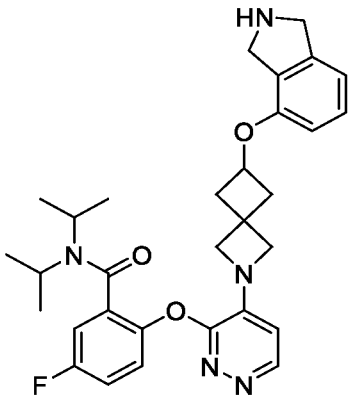
Step 6. tert-Butyl 4-((2-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



In a 50 mL round bottom flask under argon atmosphere, *tert*-butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (350 mg, 0.515 mmol) was added in MeOH (10 mL). To this solution, Pd-C (110 mg, 0.515 mmol) was added at RT, and the reaction was stirred for 8 h under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (100% EtOAc). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 60% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (250 mg, 67.6% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 5.5 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.13 – 7.07 (m, 1H), 6.97 (dd, *J* = 2.9,

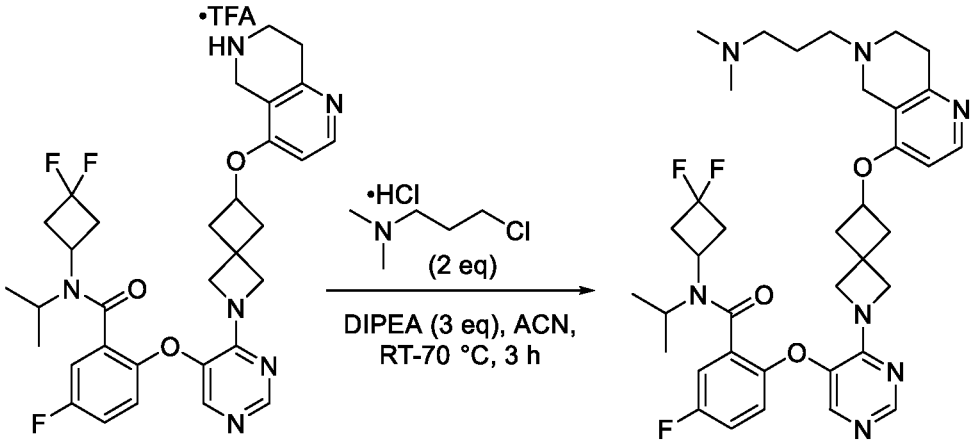
7.8 Hz, 1H), 6.90 – 6.81 (m, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.20 (d, *J* = 5.5 Hz, 1H), 4.74 – 4.56 (m, 6H), 4.52 – 4.21 (m, 3H), 3.94 – 3.81 (m, 1H), 3.46 – 3.36 (m, 1H), 2.89 – 2.73 (m, 2H), 2.57 – 2.32 (m, 2H), 1.57 – 1.50 (m, 12H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 6.5 Hz, 3H); LCMS (Method H): Rt = 2.04 min, m/z = 646.4 $[M+H]^+$; 89.83%.

Step 7. 5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-N,N-diisopropylbenzamide



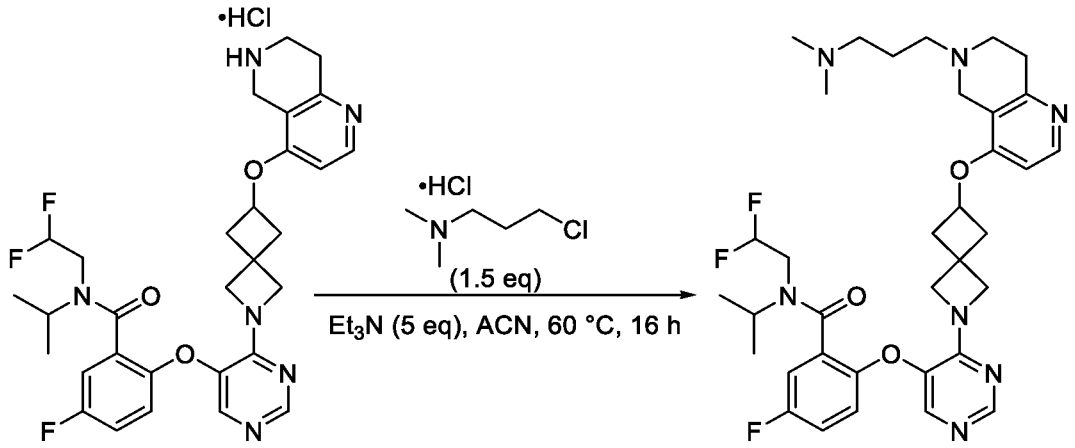
To a solution of *tert*-butyl 4-((2-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate (240 mg, 0.372 mmol) in 2,2,2-trifluoroethanol (5 mL), TMSCl (0.5 mL, 3.91 mmol) was added at 0 °C. The reaction was stirred at RT for 4 h and monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure to obtain crude 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*,*N*-diisopropylbenzamide hydrochloride. The crude product was purified by Prep HPLC (Method J) to obtain 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*,*N*-diisopropylbenzamide (69.28 mg, 34.1% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, *J* = 5.4 Hz, 1H), 7.36 – 7.22 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 5.5 Hz, 1H), 4.74 – 4.66 (m, 1H), 4.31 – 4.10 (m, 4H), 4.04 (s, 2H), 3.99 (s, 2H), 3.60 (quin, *J* = 6.4 Hz, 1H), 3.50 – 3.35 (m, 1H), 2.81 – 2.70 (m, 2H), 2.31 – 2.20 (m, 2H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.56 (d, *J* = 6.5 Hz, 3H), -NH peak merged with solvent peak; LCMS (Method D): Rt = 1.89 min, m/z = 546.2 $[M+H]^+$; HPLC (Method A): Rt = 5.18 min, 99.81%.

Example 14. *N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 176)



To a stirred solution of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate (150 mg, 0.207 mmol) and 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride (78 mg, 0.493 mmol) in ACN (5 mL), DIPEA (0.129 mL, 0.739 mmol) was added at RT. The reaction was stirred at 70 °C for 3 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford the crude compound. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-(3,3-difluorocyclobutyl)-2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (15 mg, 10.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.35 (dd, J = 2.9, 8.0 Hz, 1H), 7.27 (dt, J = 2.9, 8.6 Hz, 1H), 7.06 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.74 (quin, J = 6.6 Hz, 1H), 4.35 - 4.03 (m, 4H), 3.98 - 3.83 (m, 1H), 3.83 - 3.45 (m, 3H), 3.45 - 3.36 (m, 2H), 2.87 - 2.61 (m, 9H), 2.31 - 2.18 (m, 4H), 2.12 (s, 6H), 1.62 (quin, J = 7.2 Hz, 2H), 1.51 - 1.27 (m, 1H), 1.15 - 0.96 (m, 6H); LCMS (Method B): Rt = 1.44 min, m/z = 694.2 $[M+H]^+$; HPLC (Method A): Rt = 5.20 min, 99.16%.

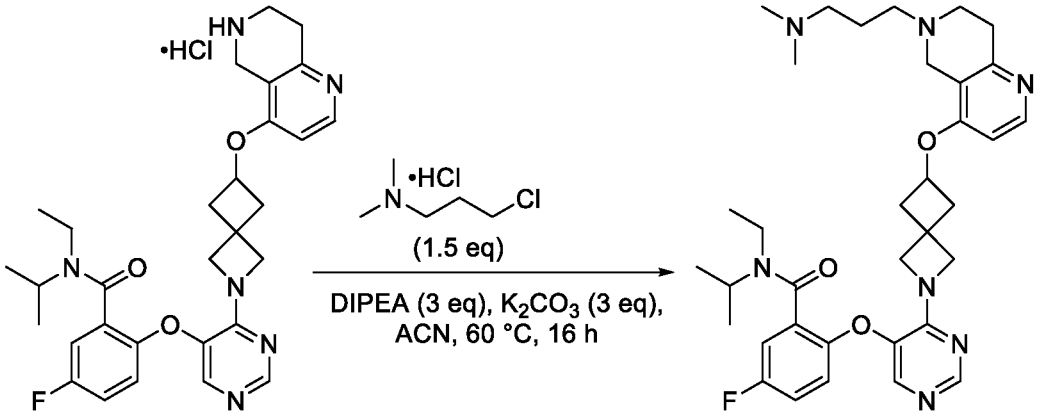
Example 15. *N*-(2,2-Difluoroethyl)-2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 85)



This compound was synthesized following the procedure described for the synthesis of Example 14 starting with *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 5 equivalents of TEA and 1.5 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride were used. The reaction was stirred at 60 °C. The crude compound was purified by Prep HPLC (Method M) to afford *N*-(2,2-difluoroethyl)-2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide.

Yield: 9.32%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.28 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.83 – 7.71 (m, 1H), 7.29 – 7.25 (m, 2H), 7.06 – 6.99 (m, 1H), 6.63 (d, J = 5.7 Hz, 1H), 6.34 – 6.06 (m, 1H), 4.81 – 4.69 (m, 1H), 4.27 – 4.13 (m, 4H), 3.98 – 3.83 (m, 1H), 3.79 – 3.66 (m, 2H), 3.45 (s, 2H), 2.85 – 2.64 (m, 6H), 2.55 – 2.52 (m, 2H), 2.36 – 2.23 (m, 4H), 2.15 (br s, 6H), 1.65 (p, J = 7.2 Hz, 2H), 1.13 (br s, 6H); LCMS (Method G): Rt = 1.78 min, m/z = 668.3 $[M+H]^+$; HPLC (Method A): Rt = 4.96 min, 98.41%.

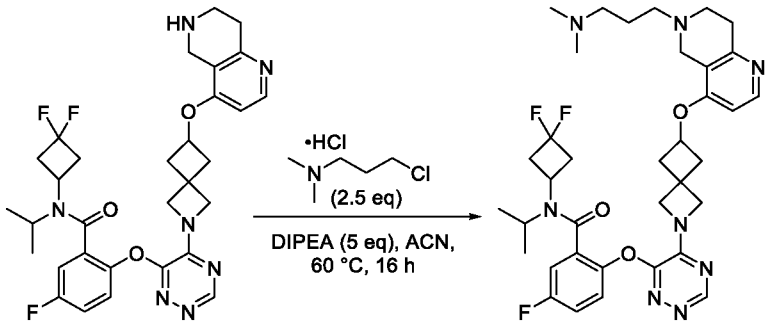
Example 16. 2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 65)



This compound was synthesized following the procedure described for the synthesis of Example 14 starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride was used. The reaction was stirred at 60 °C. The crude compound was purified by Prep HPLC (Method D) to afford 2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 23.79%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 – 8.26 (m, 1H), 8.21 – 8.13 (m, 1H), 7.75 – 7.66 (m, 1H), 7.33 – 7.21 (m, 2H), 7.10 – 7.00 (m, 1H), 6.69 – 6.63 (m, 1H), 4.82 – 4.68 (m, 1H), 4.33 – 4.04 (m, 4H), 3.81 – 3.73 (m, 1H), 3.43 – 3.38 (m, 3H), 3.29 – 3.21 (m, 2H), 2.83 – 2.73 (m, 4H), 2.73 – 2.64 (m, 3H), 2.37 – 2.15 (m, 4H), 2.12 (s, 6H), 1.69 – 1.55 (m, 2H), 1.28 – 0.81 (m, 9H); LCMS (Method D): Rt = 1.66 min, m/z = 632.4 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 99.74%.

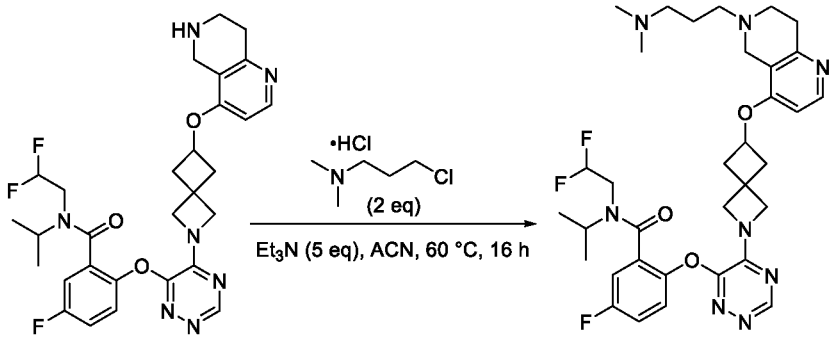
Example 17. *N*-(3,3-Difluorocyclobutyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 187) – Procedure A



This compound was synthesized following the procedure described for the synthesis of Example 14 starting with *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 5 equivalents of DIPEA and 2.5 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride were used. The reaction was stirred at 60 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford *N*-(3,3-difluorocyclobutyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide.

Yield: 48.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.54 – 7.21 (m, 3H), 6.74 – 6.62 (m, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.71 – 4.45 (m, 2H), 4.20 (m, 2H), 3.93 – 3.44 (m, 3H), 3.42 (s, 2H), 2.96 – 2.59 (m, 10H), 2.55 – 2.52 (m, 2H), 2.39 – 2.18 (m, 3H), 2.12 (br s, 6H), 1.63 (br s, 2H), 1.20 – 0.59 (m, 6H); LCMS (Method D): Rt = 1.78 min, m/z = 695.5 $[M+H]^+$; HPLC (Method F): Rt = 5.54 min, 97.81%.

Example 18. *N*-(2,2-Difluoroethyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 88)

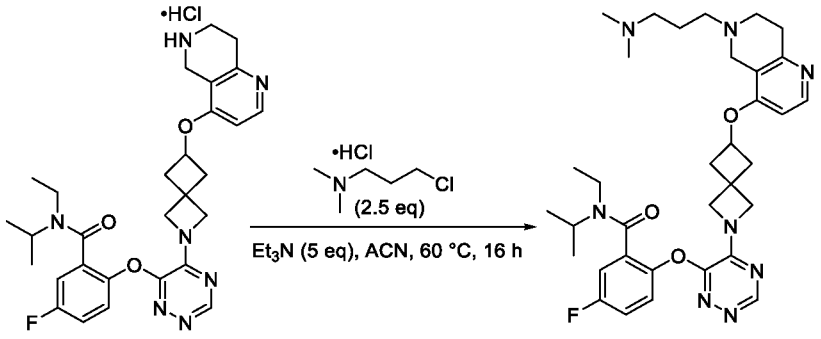


This compound was synthesized following the procedure described for the synthesis of Example 14 starting with *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-

yl)oxy)benzamide, except that 5 equivalents of TEA was used. The reaction was stirred at 60 °C. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The residue was diluted with water (25 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford *N*-(2,2-difluoroethyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide.

Yield: 62.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 –8.46 (m, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.53 – 7.33 (m, 3H), 6.69 (d, J = 5.6 Hz, 1H), 6.37 – 5.98 (m, 1H), 4.85 – 4.75 (m, 1H), 4.74 – 4.35 (m, 2H), 4.30 – 4.13 (m, 2H), 3.86 – 3.68 (m, 2H), 3.66 – 3.50 (m, 3H), 3.42 (s, 2H), 2.90 – 2.75 (m, 4H), 2.73 – 2.64 (m, 3H), 2.39 – 2.20 (m, 2H), 2.14 (br s, 6H), 1.63 (br s, 3H), 1.26 – 0.60 (m, 6H); LCMS (Method B): Rt = 1.44 min, m/z = 669.1 $[M+H]^+$; HPLC (Method A): Rt = 5.01 min, 98.77%.

Example 19. 2-((5-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 89)

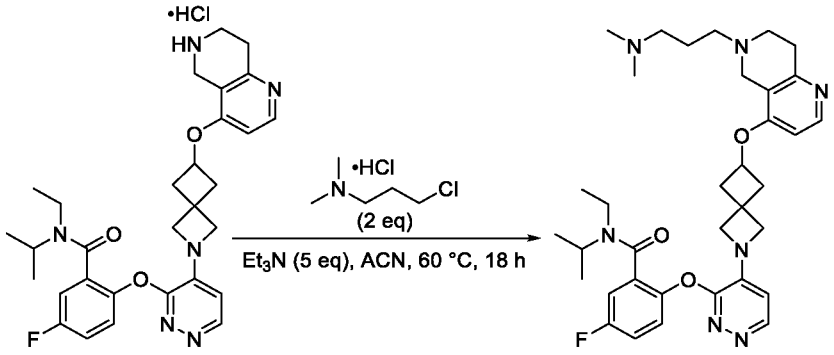


This compound was synthesized following the procedure described for the synthesis of Example 14 starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride, except that 5 equivalents of TEA and 2.5 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride were used. The reaction was stirred at 60 °C. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The residue was diluted with water (25 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous sodium sulfate,

and filtered, and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford 2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 38.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.52 – 7.28 (m, 3H), 6.68 (d, J = 5.6 Hz, 1H), 4.79 (p, J = 6.6 Hz, 1H), 4.70 – 4.46 (m, 2H), 4.40 – 4.12 (m, 2H), 3.70 – 3.56 (m, 1H), 3.49 – 3.32 (m, 4H), 3.20 – 2.97 (m, 1H), 2.88 – 2.62 (m, 7H), 2.42 – 2.18 (m, 4H), 2.12 (s, 6H), 1.72 – 1.56 (m, 2H), 1.18 – 0.66 (m, 9H); LCMS (Method B): Rt = 1.36 min, m/z = 633.2 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 99.78%.

Example 20. 2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 229)

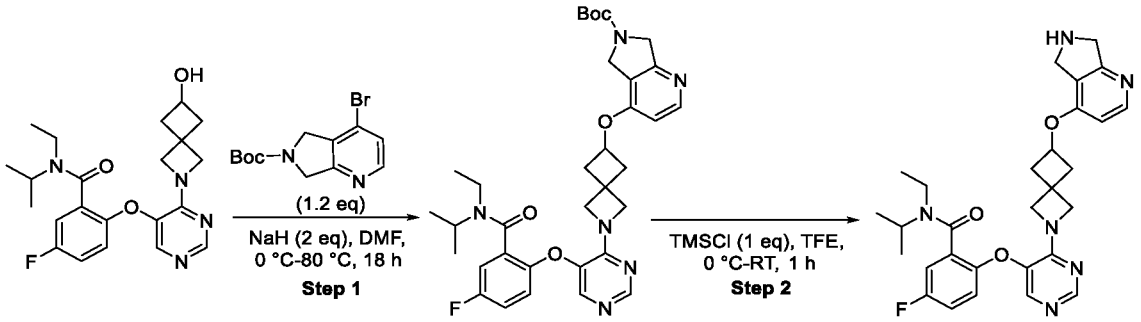


This compound was synthesized following the procedure described for the synthesis of Example 14 starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)benzamide hydrochloride, except that 5 equivalents of TEA was used. The reaction was stirred at 60 °C. The crude compound was purified by Prep HPLC (Method K), and pure fractions were concentrated under reduced pressure. ^{1}HNMR of this compound showed impurity peaks. Therefore, the material was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

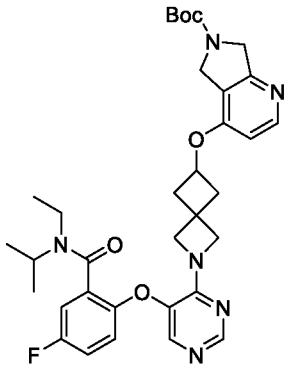
Yield: 10.20%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, J = 5.4 Hz, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.39 – 7.23 (m, 3H), 6.68 (d, J = 5.8 Hz, 1H), 6.45 (dd, J = 5.5, Hz, 1H), 4.78

(quin, *J* = 6.6 Hz, 1H), 4.36 – 4.06 (m, 4H), 3.68 (spt, *J* = 6. Hz, 1H), 3.42 (s, 2H), 3.39 – 3.36 (m, 1H), 3.11 – 3.01 (m, 1H), 2.80 – 2.79 (m, 4H), 2.71 – 2.63 (m, 2H), 2.51 – 2.50 (m, 2H), 2.35 – 2.27 (m, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 2.12 (s, 6H), 1.63 (quin, *J* = 7.2 Hz, 2H), 1.30 – 0.59 (m, 9H); LCMS (Method D): Rt = 1.68 min, m/z = 632.4 $[M+H]^+$; HPLC (Method A): Rt = 4.38 min, 99.65%.

Example 21. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-Azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 4)



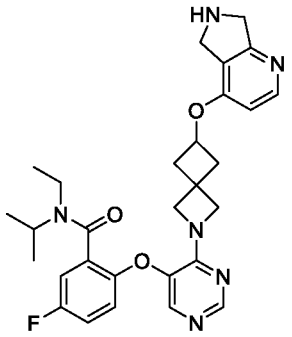
Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



In a 25 mL two neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (300 mg, 0.724 mmol) was added in DMF (10 mL). To this reaction mixture, NaH (34.7 mg, 1.448 mmol) was added at 0 °C, and the reaction was stirred at RT for 30 min. To this reaction mixture, *tert*-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (260 mg, 0.869 mmol) was added at 0 °C, and the reaction was stirred at 80 °C for 18 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine solution (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 4-((2-(5-(2-

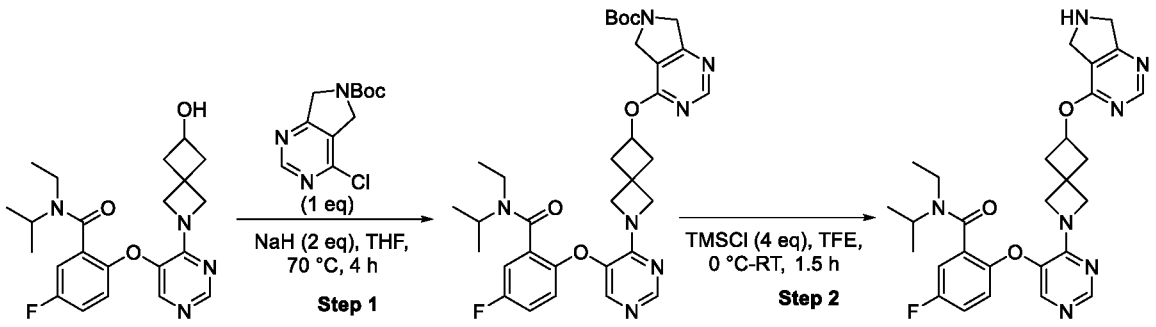
(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (500 mg, 64.5% yield). LCMS (Method D): Rt = 2.0 min, m/z = 633.4 $[M+H]^+$, 59.05%. This material was used without further purification.

Step 2. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-Azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

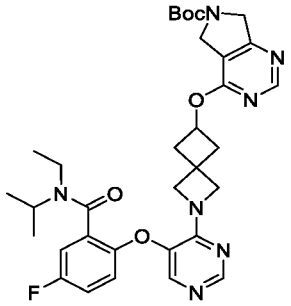


In a 50 mL single neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (500 mg, 0.790 mmol) was added in 2,2,2-trifluoroethanol (5 mL). To this reaction mixture, TMSCl (0.101 mL, 0.790 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude was purified by Prep HPLC (Method B) to afford 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (146 mg, 34.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.23 – 8.19 (m, 1H), 7.78 - 7.65 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.71 - 6.66 (m, 1H), 4.84 - 4.72 (m, 1H), 4.53 - 4.38 (m, 1H), 4.33 - 4.07 (m, 4H), 4.05 - 3.98 (m, 3H), 3.81 - 3.67 (m, 1H), 3.45 - 3.39 (m, 1H), 3.28 - 3.22 (m, 2H), 2.85 - 2.72 (m, 2H), 2.31 - 2.20 (m, 2H), 1.38 - 0.90 (m, 9H); LCMS (Method D): Rt = 1.47 min, m/z = 533.4 $[M+H]^+$; HPLC (Method A): Rt = 4.38 min, 99.93%.

Example 22. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 2)



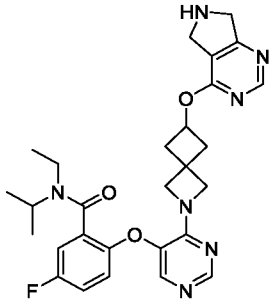
Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 21, step 1, except that 1 equivalent of *tert*-butyl 4-chloro-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate was used, and THF was used as the solvent. The reaction was stirred at 70 °C. After completion, the reaction was cooled to 0 °C, quenched with saturated ammonium chloride solution (25 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate. This material was used without further purification.

Yield: 88%; LCMS (Method D): Rt = 2.08 min, m/z = 634.2 $[M+H]^+$, 82.43%.

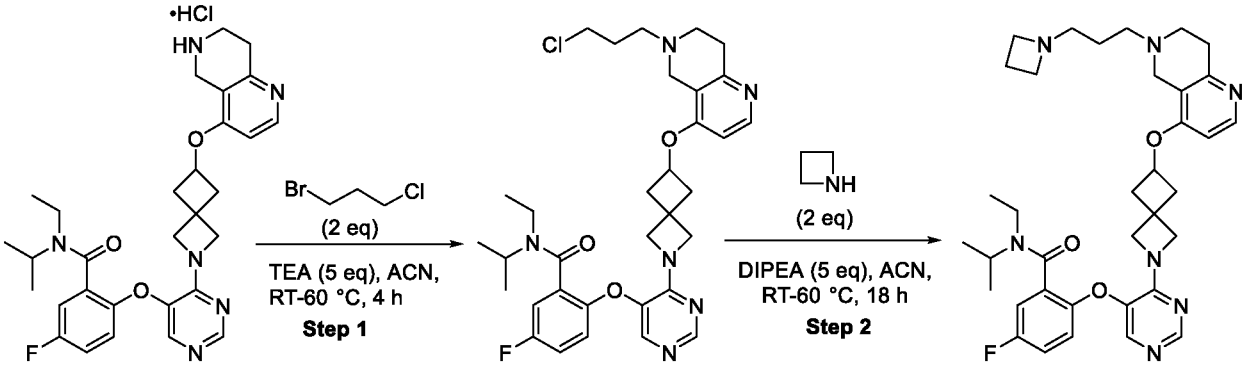
Step 2. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



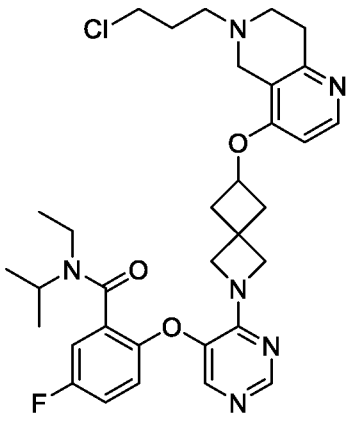
This compound was synthesized following the procedure described for the synthesis of Example 21, step 2, except that 4 equivalents of TMSCl was used to obtain crude 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude product was purified by Prep HPLC (Method D) to afford 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.29 – 8.27 (m, 1H), 7.76 – 7.68 (m, 1H), 7.34 – 7.21 (m, 2H), 7.09 – 6.97 (m, 1H), 5.20 (quin, J = 6.7 Hz, 1H), 4.52 – 4.39 (m, 1H), 4.30 – 4.08 (m, 4H), 4.05 – 3.95 (m, 4H), 3.84 – 3.71 (m, 1H), 3.49 – 3.37 (m, 1H), 3.26 – 3.19 (m, 1H), 2.81 – 2.70 (m, 2H), 2.36 – 2.25 (m, 2H), 1.31 – 0.94 (m, 9H); -NH proton not observed. LCMS (Method D) Rt = 1.53 min, m/z = 534.3 $[M+H]^+$; HPLC (Method A): Rt = 4.36 min, 98.78%.

Example 23. 2-((4-(6-((6-(3-(Azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 92)

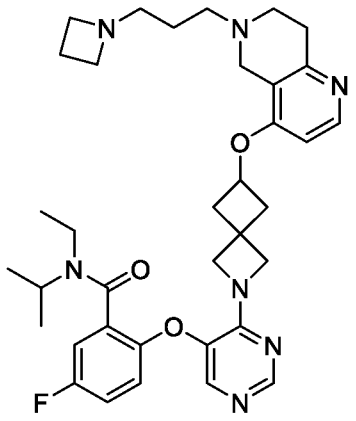


Step 1. 2-((4-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



In a 30 mL pressure vial, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (300 mg, 0.514 mmol) was added in acetonitrile (5 mL). To this solution, TEA (0.359 mL, 2.57 mmol) and 1-bromo-3-chloropropane (0.102 mL, 1.029 mmol) were added at RT. The reaction was heated to 60 °C and stirred for 4 h. The reaction progress was monitored by TLC (20% MeOH in DCM). When complete, the reaction was concentrated under reduced pressure. Water (10 mL) was added, and the mixture was extracted with DCM (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted in 8% MeOH in DCM) to obtain 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide (100 mg, 31.2% yield) as a solid. LCMS (Method B): Rt = 1.68 min, m/z = 623.3 $[M+H]^+$; 91.86%.

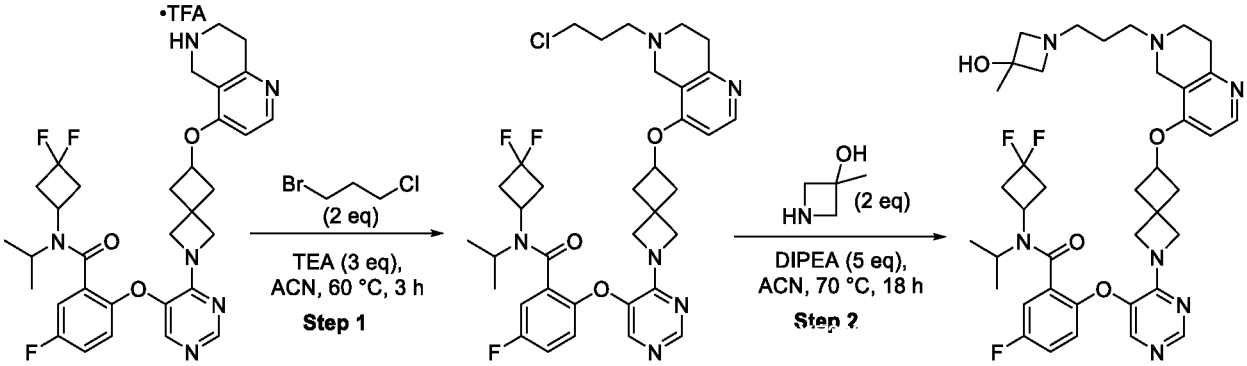
Step 2. 2-((4-(6-((6-(3-(Azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



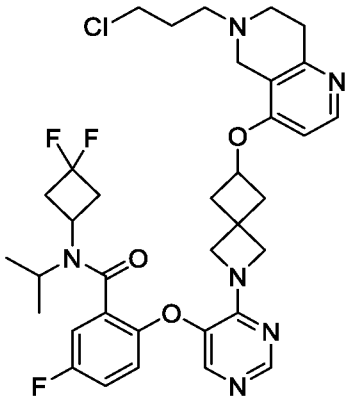
To a solution of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (100 mg, 0.160 mmol) in acetonitrile (2 mL), DIPEA (0.140 mL, 0.802 mmol) and azetidine (18.32 mg, 0.321 mmol) were added at RT. The reaction was stirred at 60 °C for 18 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude product. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(3-(azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (32.99

mg, 31.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.25 (m, 1H), 8.20 – 8.16 (m, 1H), 7.76 – 65 (m, 1H), 7.34 – 7.21 (m, 2H), 7.12 – 7.00 (m, 1H), 6.68 – 6.64 (m, 1H), 4.80 – 4.69 (m, 1H), 4.47 – 4.06 (m, 4H), 3.81 – 3.70 (m, 1H), 3.44 – 3.37 (m, 3H), 3.28 – 3.11 (m, 2H), 3.04 (t, J = 6.9 Hz, 4H), 2.84 – 2.74 (m, 4H), 2.69 – 2.63 (m, 2H), 2.48 – 2.43 (m, 1H), 2.36 – 2.22 (m, 4H), 1.92 (quin, J = 6.9 Hz, 2H), 1.47 (quin, J = 7.2 Hz, 2H), 1.24 – 0.98 (m, 9H); LCMS (Method G): Rt = 1.79 min, m/z = 644.6 $[M+H]^+$; HPLC (Method A): Rt = 4.67 min, 99.06%.

Example 24. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 214)



Step 1. 2-((4-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

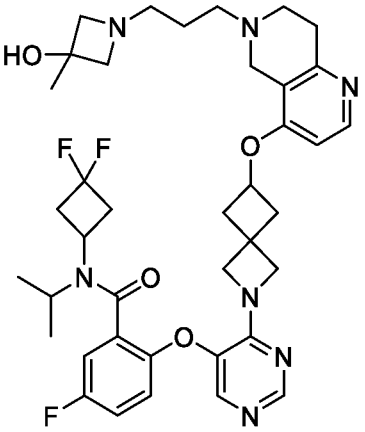


This compound was synthesized following the procedure described for the synthesis of Example 23, step 1, starting with *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate, except that 3 equivalents of TEA was used. The reaction was concentrated under reduced pressure to obtain the crude product. The crude

product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted in 5-6% MeOH in DCM) to afford 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide.

Yield: 12.29%; LCMS (Method D): Rt = 2.09 min, m/z = 685.1 $[M+H]^+$; 73.45%.

Step 2. N-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

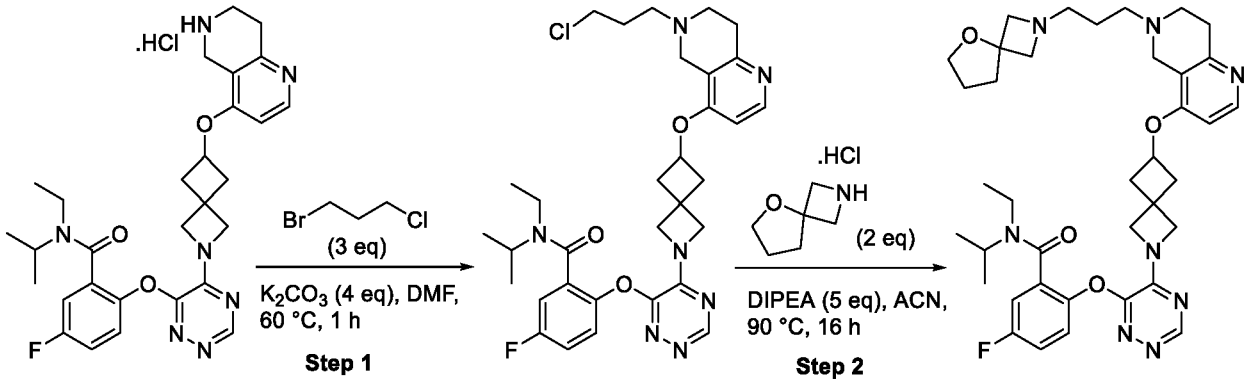


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The impure product was re-purified by Prep-HPLC (Method B) to afford *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

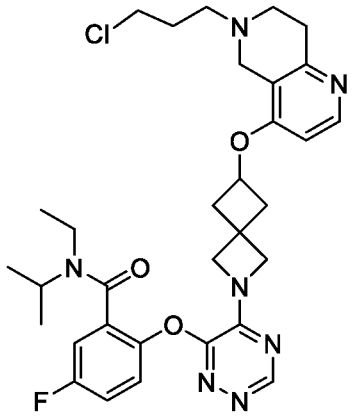
Yield: 39.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, *J* = 2.9, 8.2 Hz, 1H), 7.30 – 7.21 (m, 1H), 7.06 (dd, *J* = 4.3, 9.0 Hz, 1H), 6.66 (d, *J* = 5.8 Hz, 1H), 5.11 (s, 1H), 4.74 (quin, *J* = 6.6 Hz, 1H), 4.35 – 4.06 (m, 4H), 3.97 – 3.35 (m, 5H), 3.39 (s, 2H), 2.83 – 2.64 (m, 9H), 2.48 – 2.41 (m, 4H), 2.26 – 2.22 (m, 3H), 1.56 – 1.41 (m, 3H), 1.33 (s, 3H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); LCMS (Method G): Rt = 1.74 min, m/z = 734.6 $[M-H]^-$; HPLC (Method E): Rt = 3.10 min, 99.06%.

Example 25. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 299)

First Procedure:



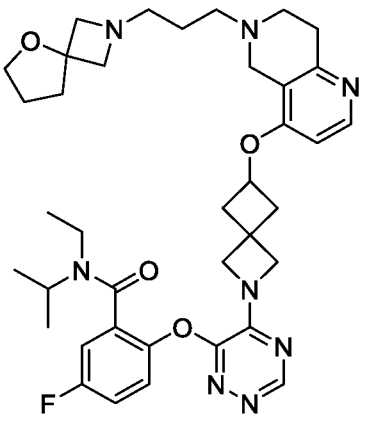
Step 1. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 23, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride, except that 4 equivalents of K_2CO_3 and 3 equivalents of 1-bromo-3-chloropropane were used in DMF as a solvent. After completion, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide. This material was used without further purification.

Yield: 61.4%; LCMS (Method B): Rt = 1.19 min, m/z = 624.3 $[M+H]^+$; 78.76%.

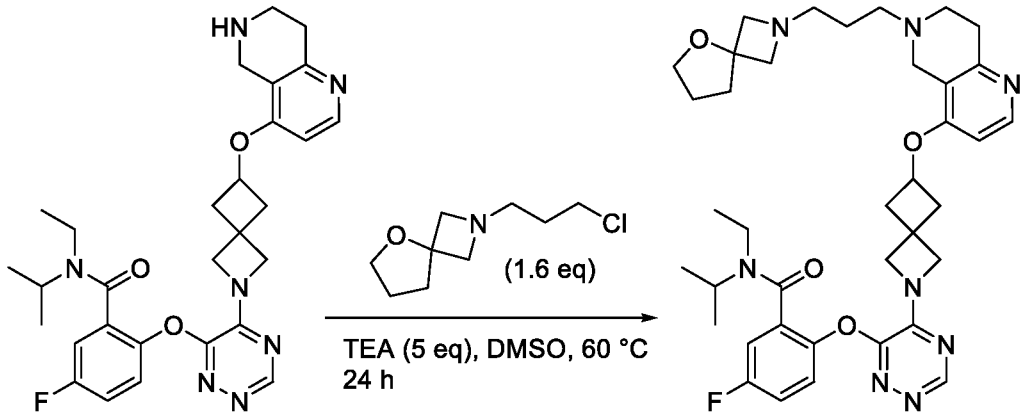
Step 2. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2. The reaction was stirred at 90 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford an impure product. The material was re-purified by prep HPLC (Method-N) to afford 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 16.83%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.47 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.68 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.5 Hz, 1H), 4.67 - 4.48 (m, 2H), 4.27 - 4.11 (m, 2H), 3.69 - 3.57 (m, 3H), 3.40 (s, 2H), 3.27 - 3.19 (m, 3H), 3.13 - 3.00 (m, 1H), 2.93 - 2.77 (m, 6H), 2.67 - 2.64 (m, 2H), 2.42 - 2.37 (m, 2H), 2.02 - 1.95 (m, 2H), 1.84 - 1.76 (m, 2H), 1.55 - 1.45 (m, 2H), 1.17 - 0.68 (m, 9H), four protons merged with solvent peak; LCMS (Method G): Rt = 1.69 min, m/z = 701.4 $[M+H]^+$; HPLC (Method A): Rt = 4.81 min, 99.86%.

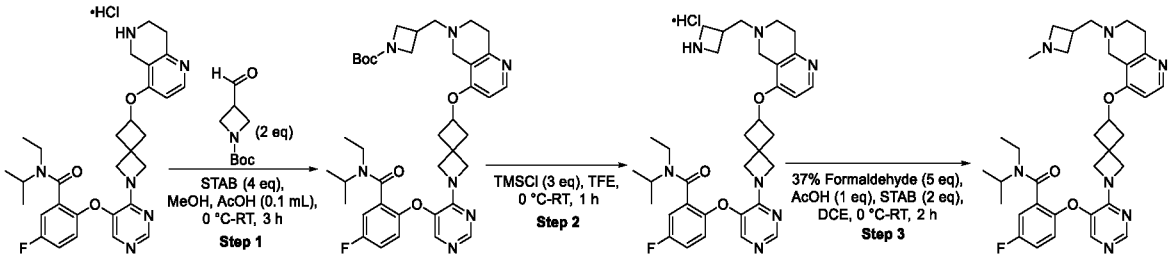
Second Procedure:



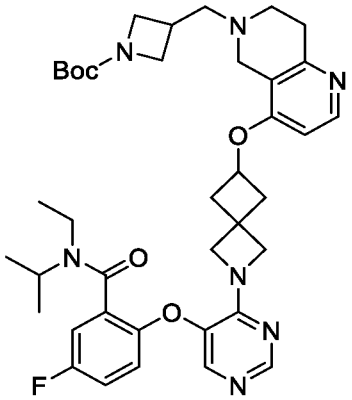
In a 40 mL pressure vial, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (500 mg, 0.913 mmol) and 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (277 mg, 1.461 mmol)

were added in DMSO (10 mL) under a nitrogen atmosphere. To this solution, triethylamine (0.636 mL, 4.57 mmol) was added at RT. The reaction was stirred at 60 °C for 24 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to remove DMSO. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (350 mg, 53.4 % yield)) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 6.68 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.69 - 4.48 (m, 2H), 4.33 - 4.11 (m, 2H), 3.69 - 3.58 (m, 3H), 3.40 (br s, 2H), 3.29 - 3.21 (m, 3H), 3.16 - 2.98 (m, 1H), 2.92 - 2.76 (m, 6H), 2.70 - 2.62 (m, 2H), 2.47 - 2.33 (m, 4H), 2.02 - 1.94 (m, 2H), 1.80 (quin, J = 6.8 Hz, 2H), 1.50 (br s, 2H), 1.19 - 0.64 (m, 9H), two protons merged with solvent peaks; LCMS (Method A): Rt = 1.74 min, m/z = 701.5 $[M+H]^+$; HPLC (Method A): Rt = 4.83 min, 97.57%.

Example 26. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 75)

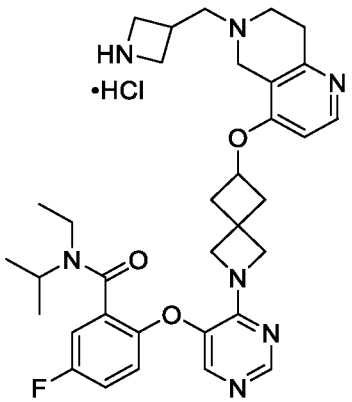


Step 1. tert-Butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.2 g, 0.366 mmol) in methanol (4 mL), *tert*-butyl 3-formylazetidine-1-carboxylate (0.136 g, 0.732 mmol) and AcOH (0.1 mL) were added at 0 °C. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (0.310 g, 1.463 mmol) was added at 0 °C, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 3-5% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate (0.250 g, 85% yield) as a solid. LCMS (Method D): Rt 1.95 min, m/z = 716.6 $[M+H]^+$, 89.40%.

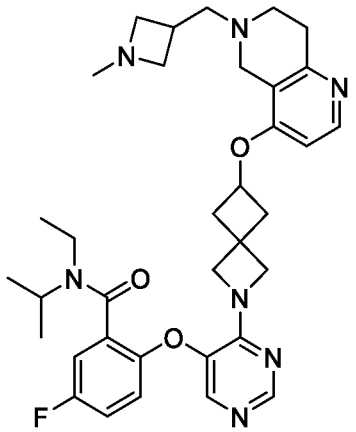
Step 2. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-Tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



In a 50 mL single neck round bottom flask under nitrogen atmosphere, *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-

azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate (0.2 g, 0.279 mmol) was added in 2,2,2-trifluoroethanol (10 mL). To this reaction mixture, TMSCl (0.107 mL, 0.838 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.168 g, 91% yield) as a solid. LCMS (Method B): Rt = 1.34 min, m/z = 616.0 $[M+H]^+$, 93.28%. This material was used without further purification.

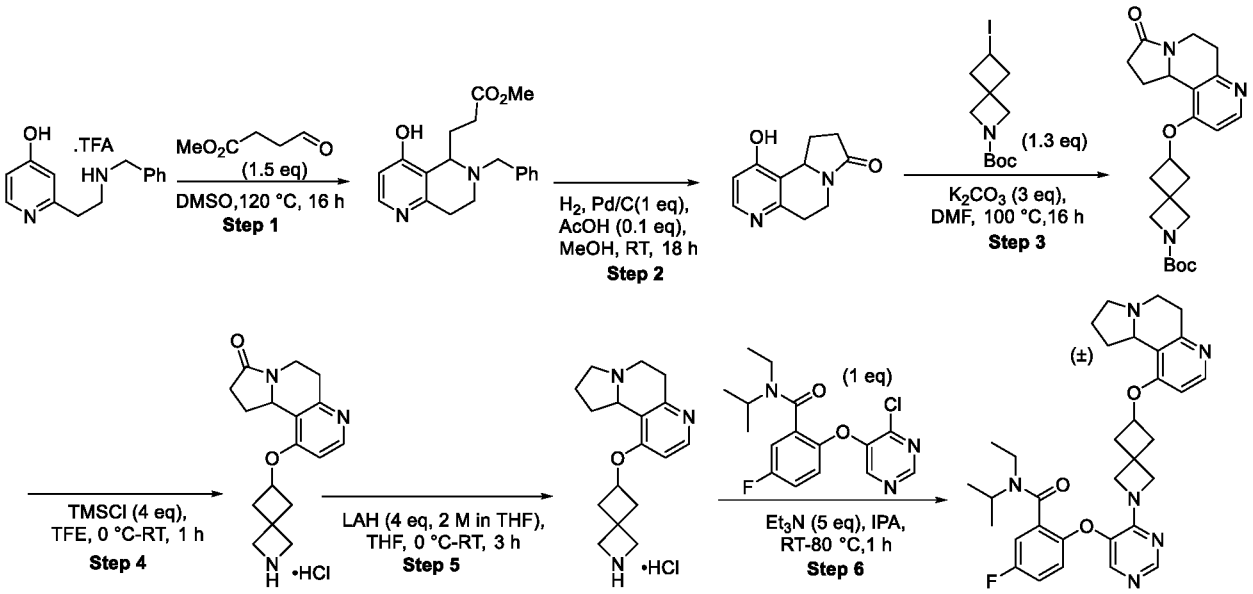
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



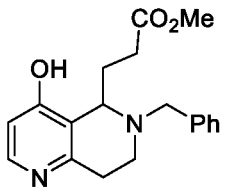
In a 50 mL single neck round bottom flask under nitrogen atmosphere, 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.165 g, 0.268 mmol) was added in DCE (5 mL). To this reaction mixture, formaldehyde (0.100 mL, 1.340 mmol, 37% in H_2O) and acetic acid (0.015 mL, 0.268 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (0.114 g, 0.536 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by crude LCMS (Method E): Rt = 0.92 min, m/z= 630.6 $[M+H]^+$, 86.53%. After completion, the reaction was concentrated under reduced pressure to afford the crude compound. The crude product was purified by Prep HPLC (Method A) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (57.69 mg, 35.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32

- 8.25 (m, 1H), 8.20 - 8.13 (m, 1H), 7.80 - 7.63 (m, 1H), 7.35 - 7.20 (m, 2H), 7.12 - 6.96 (m, 1H), 6.69 - 6.62 (m, 1H), 4.80 - 4.68 (m, 1H), 4.47 - 4.37 (m, 1H), 4.31 - 4.03 (m, 4H), 3.82 - 3.70 (m, 1H), 3.45 - 3.36 (m, 3H), 3.30 - 3.11 (m, 2H), 2.84 - 2.71 (m, 6H), 2.70 - 2.56 (m, 5H), 2.31 - 2.20 (m, 2H), 2.17 (m, 3H), 1.32 - 0.87 (m, 9H); LCMS (Method B): Rt 1.38 min, m/z = 630.4 $[M+H]^+$; HPLC (Method A): Rt = 4.54 min, 92.81%.

Example 27. (±)-*N*-Ethyl-5-fluoro-2-((4 (6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 241)



Step 1. (±)-Methyl 3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoate

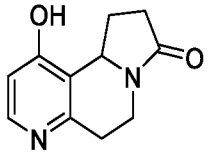


Step 1 was performed following the same procedure in four batches (4 x 500 mg).

In a 30 mL pressure vial under a nitrogen atmosphere, 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (500 mg, 1.461 mmol) was added in DMSO (12.5 mL). To this solution, methyl 4-oxobutanoate (254 mg, 2.191 mmol) was added at RT. The reaction was stirred at 120 °C for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The crude from four batches was combined for the workup. To this crude material, ice-cold water (50 mL) was added, and the mixture was extracted with 10% MeOH in DCM (3 x 50 mL). The product was found in the aqueous layer. The aqueous layer was basified with sodium bicarbonate solution (25 mL) and re-extracted with 10% MeOH in DCM

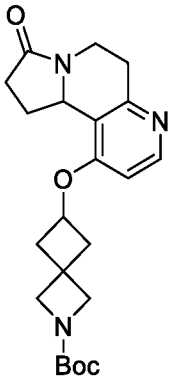
(2 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude product. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 15% MeOH in DCM) to obtain (±)-methyl 3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoate (837 mg, 43.88% combined yield) as a solid. LCMS (Method G): Rt = 1.40 min, m/z = 327.3 $[M+H]^+$; 95.84%.

Step 2. (±)-1-Hydroxy-5,9,10,10a-tetrahydropyrrolo[2,1-f][1,6]naphthyridin-8(6H)-one



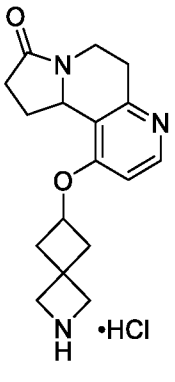
In a 100 mL round bottom flask, (±)-methyl 3-(6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propanoate (1.2 g, 3.68 mmol) was added in MeOH (23 mL) at RT. To this solution, AcOH (0.021 mL, 0.368 mmol) and Pd-C (3.91 g, 3.68 mmol) were added, and the reaction was stirred under a hydrogen atmosphere (balloon pressure) at RT for 18 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure to obtain the crude product. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were collected and concentrated under reduced pressure to afford (±)-1-hydroxy-5,9,10,10a-tetrahydropyrrolo[2,1-f][1,6]naphthyridin-8(6H)-one (480 mg, 63.91% yield) as a solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.38 (br s, 1H), 7.57 (d, J = 7.3 Hz, 1H), 6.02 (d, J = 7.0 Hz, 1H), 4.51 (t, J = 7.8 Hz, 1H), 4.17 – 4.10 (m, 1H), 2.91 – 2.74 (m, 2H), 2.70 – 2.54 (m, 2H), 2.46 – 2.32 (m, 1H), 2.20 – 2.10 (m, 1H), 1.50 – 1.36 (m, 1H); LCMS (Method D): Rt = 0.61 min, m/z = 205.1 $[M+H]^+$; 98.93%.

Step 3. (±)-tert-Butyl 6-((8-oxo-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



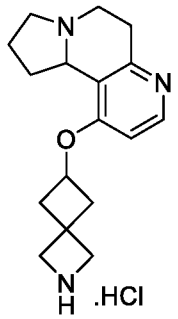
To a stirred solution of (±)-1-hydroxy-5,9,10,10a-tetrahydropyrrolo[2,1-f][1,6]naphthyridin-8(6H)-one (0.48 g, 2.350 mmol) in DMF (14.8 mL), K_2CO_3 (0.974 g, 7.05 mmol) was added at RT. The reaction was stirred at RT for 10 min. To this reaction mixture, *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (0.987 g, 3.06 mmol) was added, and the reaction was stirred at 100 °C for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). To this reaction, water (100 mL) was added, and the mixture was extracted with DCM (2 x 100 mL). The combined organic layer was washed with ice-cold water (3 x 50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to afford crude product. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((8-oxo-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.55 g, 57.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, J = 5.5 Hz, 1H), 6.76 (d, J = 5.7 Hz, 1H), 4.81 – 4.70 (m, 2H), 4.23 – 4.16 (m, 1H), 3.91 (s, 2H), 3.85 (s, 2H), 2.95 – 2.90 (m, 1H), 2.81 – 2.70 (m, 5H), 2.49 – 2.41 (m, 1H), 2.32 – 2.14 (m, 3H), 1.65 – 1.50 (m, 1H), 1.37 (s, 9H); LCMS (Method D): Rt = 1.69 min, m/z = 400.2 $[M+H]^+$; 98.01%.

Step 4. (±)-1-((2-Azaspiro[3.3]heptan-6-yl)oxy)-5,9,10,10a-tetrahydropyrrolo[2,1-f][1,6]naphthyridin-8(6H)-one hydrochloride



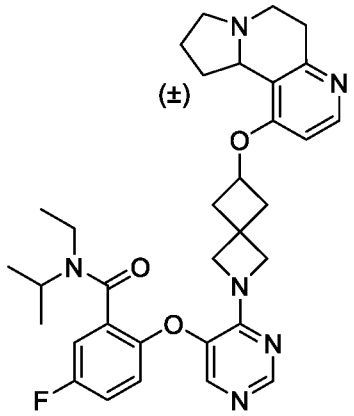
To a stirred solution of (±)-*tert*-butyl 6-((8-oxo-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.2 g, 0.501 mmol) in 2,2,2-trifluoroethanol (10 mL), TMSCl (0.256 mL, 2.003 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h and monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude compound was co-distilled with EtOAc (50 mL) and concentrated under reduced pressure to obtain crude (±)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,9,10,10a-tetrahydropyrrolo[2,1-f][1,6]naphthyridin-8(6H)-one hydrochloride (0.16 g, 92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (br s, 2H), 8.64 (br s, 1H), 7.28 (br s, 1H), 5.01 (br s, 1H), 4.80 (t, J = 8.1 Hz, 1H), 4.32 – 4.19 (m, 1H), 4.03 (t, J = 6.0 Hz, 2H), 3.98 (t, J = 6.1 Hz, 2H), 3.06 – 2.72 (m, 6H), 2.47 – 2.34 (m, 3H), 2.30 – 2.22 (m, 1H), 1.75 – 1.63 (m, 1H); LCMS (Method G): Rt = 0.99 min, m/z = 300.3 $[M+H]^+$; 97.41%. This material was used without further purification.

Step 5. (±)-1-((2-Azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridine hydrochloride



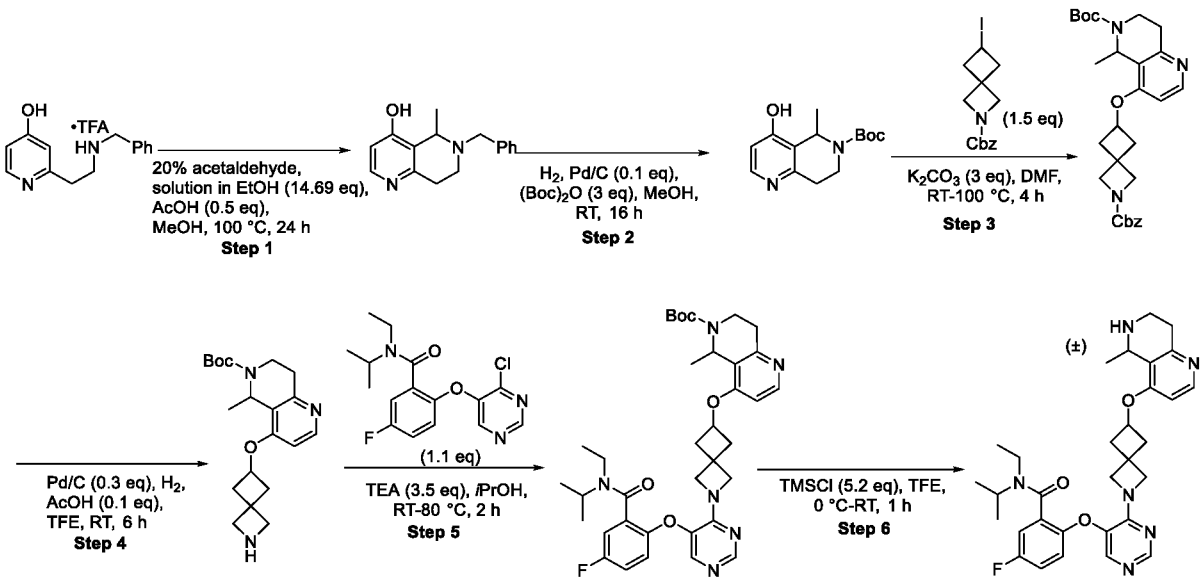
To a stirred solution of (±)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,9,10,10a-tetrahydropyrrolo[2,1-f][1,6]naphthyridin-8(6H)-one hydrochloride (0.16 g, 0.476 mmol) in dry THF (2 mL), lithium aluminum hydride (0.953 mL, 1.906 mmol, 2 M in THF) was added at 0 °C. The reaction was stirred at RT for 3 h. The reaction progress was monitored by LCMS. The reaction was quenched with the slow addition of ice-cold water (1 mL). The reaction was filtered using a syringe filter. To the residue, MeOH (2 x 10 mL) was added, and the mixture was filtered using a syringe filter. The combined filtrate was concentrated under reduced pressure to obtain crude (±)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridine hydrochloride (0.130 g, 85% yield). LCMS (Method I): Rt = 1.42 min, m/z = 286.1 $[M+H]^+$; 93.79%. This material was used without further purification.

Step 6. (±)-N-Ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

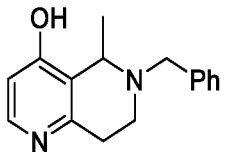


To a stirred solution of (±)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridine hydrochloride (0.13 g, 0.404 mmol) in dry 2-propanol (13 mL), triethylamine (0.281 mL, 2.020 mmol) and 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.136 g, 0.404 mmol) were added at RT. The reaction was stirred at 80 °C for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were concentrated under reduced pressure to afford (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.110 g, 40.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 – 8.24 (m, 1H), 8.17 (d, J = 5.5, Hz, 1H), 7.76 – 7.66 (m, 1H), 7.33 – 7.21 (m, 2H), 7.11 – 7.01 (m, 1H), 6.69 – 6.65 (m, 1H), 4.81 – 4.70 (m, 1H), 4.46 – 4.07 (m, 4H), 3.81 – 3.71 (m, 1H), 3.65 (t, J = 8.1 Hz, 1H), 3.46 – 3.37 (m, 1H), 3.27 – 3.11 (m, 1H), 3.01 – 2.73 (m, 6H), 2.69 – 2.60 (m, 2H), 2.45 – 2.37 (m, 1H), 2.29 – 2.17 (m, 2H), 1.85 – 1.66 (m, 2H), 1.53 – 1.40 (m, 1H), 1.22 – 0.97 (m, 9H); LCMS (Method G): Rt = 1.73 min, m/z = 587.5 $[M+H]^+$; HPLC (Method A): Rt = 5.08 min, 99.82%; SFC (Method AAW) = Peak 1: Rt = 3.02 min, 49.46%; Peak 2; Rt = 4.32 min, 50.01%.

Example 28. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 132)



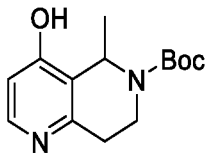
Step 1. 6-(±)-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



In an autoclave, 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (1.0 g, 2.92 mmol) was added in ethanol (20 mL). To this solution, 20% acetaldehyde solution in ethanol (11.99 mL, 42.9 mmol) and AcOH (0.084 mL, 1.461 mmol) were at RT. The reaction was heated to 100 °C and stirred for 24 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated to obtain the crude. The crude product was purified by silica gel flash column chromatography using MeOH (7% ammonia in MeOH) in DCM (product eluted in 9% MeOH in DCM) to obtain (±)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (460 mg, 37.5% yield) as a solid. LCMS (Method G): Rt = 1.23 min, m/z = 255.1 $[M+H]^+$; 60.59%.

Note: Traces of TFA remained with the product.

Step 2. (±)-tert-Butyl 4-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



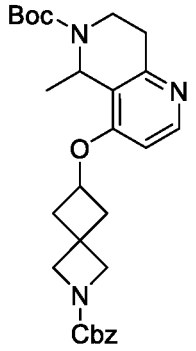
To a solution of (±)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (2 g, 7.86 mmol) in MeOH (30 mL), Pd-C (0.837 g, 0.786 mmol) and $(Boc)_2O$ (5.42 mL, 23.59 mmol) were added at RT. The reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (50% EtOAc in hexane). The reaction

was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure to obtain crude compound. The crude was triturated with 20% DCM in hexane to remove non-polar impurities and filtered. The solid was dried under reduced pressure to afford (±)-*tert*-butyl 4-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (700 mg, 33.0% yield) as a gummy solid. The filtrate was also concentrated under reduced pressure to obtain the remaining crude product (400 mg, LCMS-69.76%). This material was used without further purification.

LCMS (Method B): Rt = 1.69 min, m/z = 265.3 $[M+H]^+$; 97.86%.

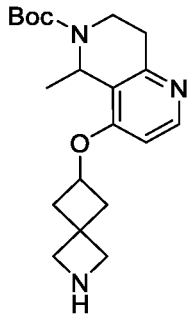
Note: Traces of TFA remained with the product.

Step 3. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



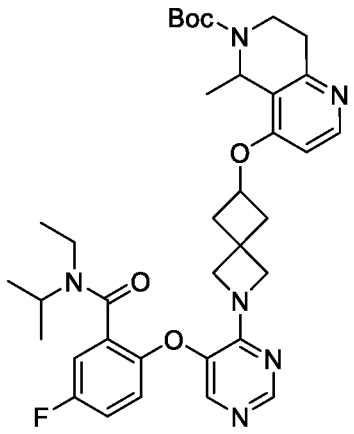
In a 20 mL pressure vial, (±)-*tert*-butyl 4-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (660 mg, 2.497 mmol) was added in DMF (8 mL). To this solution, K_2CO_3 (1035 mg, 7.49 mmol) and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (1338 mg, 3.75 mmol) were added at RT. The reaction was heated to 100 °C and stirred for 4 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layer was washed with brine solution (10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 5% MeOH in DCM). The pure fractions were concentrated under reduced pressure to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.320 g, 21.17% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 5.7 Hz, 1H), 7.42 – 7.28 (m, 5H), 6.72 (d, J = 5.7 Hz, 1H), 5.22 – 5.11 (m, 1H), 5.03 (s, 2H), 4.81 – 4.71 (m, 1H), 4.10 – 3.95 (m, 5H), 3.19 – 3.18 (m, 1H), 2.81 – 2.76 (m, 4H), 2.30 – 2.13 (m, 2H), 1.42 (s, 9H), 1.31 (d, J = 6.4 Hz, 3H); LCMS (Method B): Rt = 2.21 min, m/z = 494.2 $[M+H]^+$; 84.79%.

Step 4. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (300 mg, 0.608 mmol) in 2,2,2-trifluoroethanol (10 mL), Pd-C (200 mg, 0.188 mmol) and acetic acid (3.48 µL, 0.061 mmol) were added at RT. The reaction was stirred at RT for 6 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was bubbled with nitrogen gas for 5 min, filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (260 mg, 100% yield) as a sticky liquid. LCMS (Method B): Rt = 1.33 min, m/z = 360.2 $[M+H]^+$; 84.52%. This material was used without further purification.

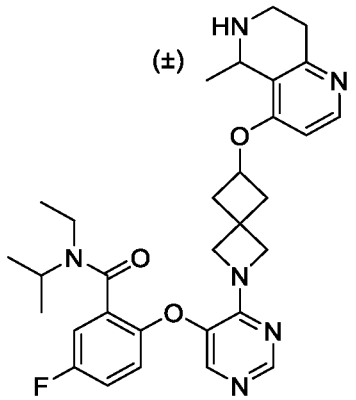
Step 5. (±)-tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a solution of (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (260 mg, 0.723 mmol) and 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (269 mg, 0.796 mmol) in

2-propanol (10 mL), TEA (0.353 mL, 2.53 mmol) was added at RT. The reaction was stirred at 80 °C for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (300 mg, 54.1% yield) as yellowish solid. LCMS (Method B): Rt = 2.02 min, m/z = 661.4 $[M+H]^+$; 86.17%.

Step 6. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

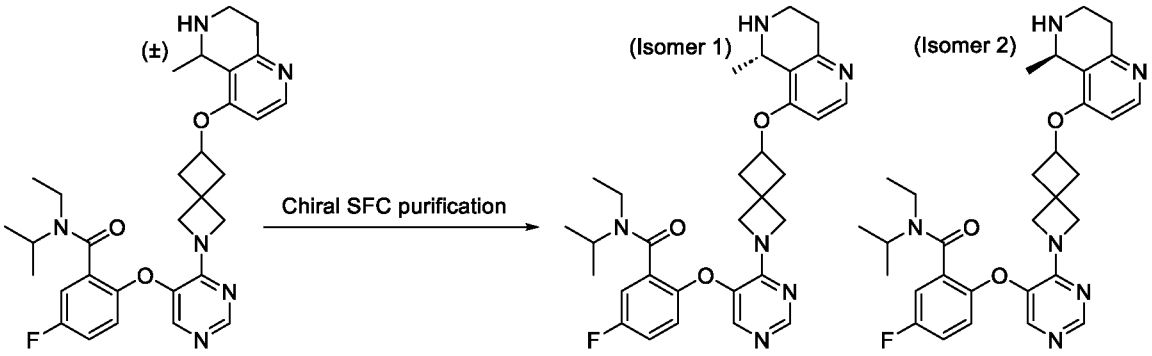


To a solution of (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (300 mg, 0.454 mmol) in 2,2,2-trifluoroethanol (10 mL), TMSCl (0.3 mL, 2.347 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude product. The crude was triturated with EtOAc (25 mL), filtered, and the residue was dried under reduced pressure to obtain crude (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (150 mg, 58.6% yield) as a solid. 1H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.64 (br d, J = 5.5 Hz, 1H), 4.85 – 4.63 (m, 1H), 4.47 - 4.16 (m, 3H), 4.14 - 4.03 (m, 2H), 3.81 - 3.71 (m, 1H), 3.45 - 3.38 (m, 1H),

3.26 - 3.20 (m, 1H), 3.18 - 3.04 (m, 2H), 2.93 - 2.75 (m, 3H), 2.69 - 2.63 (m, 2H), 2.29 – 2.17 (m, 2H), 1.28 (br d, *J* = 6.5 Hz, 3H), 1.23 - 0.97 (m, 9H). LCMS (Method B): Rt = 1.35 min, m/z = 561.6 [M+H]+; HPLC (Method A): Rt = 5.15 min, 95.71%; Chiral SFC (Method Y): Peak 1: Rt = 5.55 min, 43.32%; Peak 2: Rt = 6.49 min, 44.09%; LCMS (Method B): Rt = 1.35 min, m/z = 561.6 $[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 95.71%; Chiral SFC (Method Y): Peak 1: Rt = 5.55 min, 43.32%; Peak 2: Rt = 6.49 min, 44.09%.

Example 29. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 149)

Example 30. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 150)



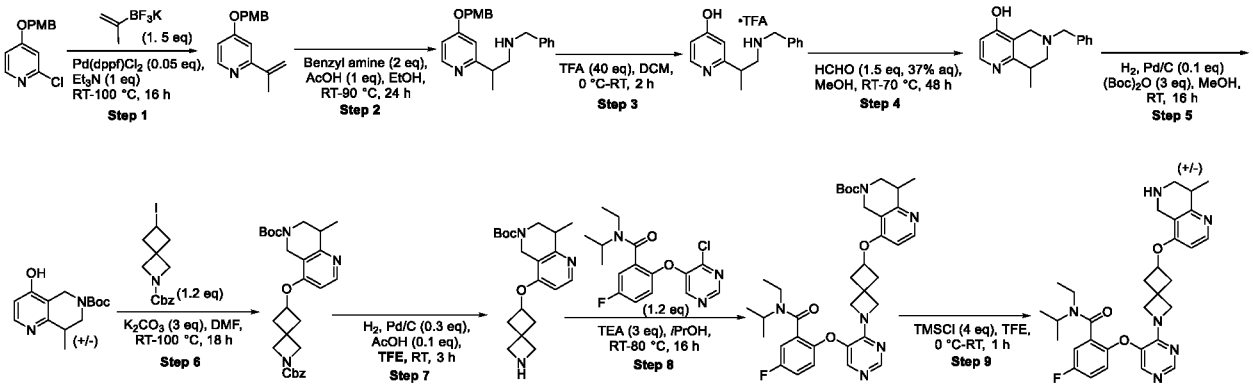
(±) *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (150 mg) was purified by chiral Prep SFC (Method A). ^{1}H NMR showed impurities in both separated compounds. Therefore, Isomer 1 and Isomer 2 were re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain both isomers, (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (19.32 mg, 12.86 % yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (30.07 mg, 19.88% yield) as solids.

Isomer 1: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 - 8.12 (m, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.68 - 6.62 (m, 1H), 4.78 - 4.69 (m, 1H), 4.46 - 4.17 (m, 3H), 4.15 - 4.01 (m, 2H), 3.81 - 3.70 (m, 1H), 3.47 - 3.37 (m, 1H), 3.28 - 3.20 (m, 1H), 3.19 - 3.03 (m, 2H), 2.95 - 2.74 (m, 3H), 2.66 - 2.60 (m, 2H), 2.28 – 2.15

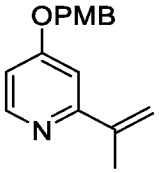
(m, 2H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.56 min, m/z = 561.5 $[M+H]^+$; 99.86%; HPLC (Method A): Rt = 5.16 min, 99.87%; Chiral SFC (Method A): Rt = 5.45 min, 100%.

Isomer 2: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.16 - 8.14 (m, 1H), 7.76 - 7.65 (m, 1H), 7.33 - 7.23 (m, 2H), 7.11 - 7.00 (m, 1H), 6.67 - 6.62 (m, 1H), 4.79 - 4.70 (m, 1H), 4.43 - 4.16 (m, 3H), 4.14 - 4.02 (m, 2H), 3.80 - 3.68 (m, 1H), 3.45 - 3.38 (m, 1H), 3.28 - 3.21 (m, 1H), 3.18 - 3.02 (m, 2H), 2.94 - 2.74 (m, 3H), 2.66 - 2.59 (m, 2H), 2.27 – 2.18 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.56 min, m/z = 561.5 $[M+H]^+$; 99.74%; HPLC (Method A): Rt = 5.17 min, 99.14%; Chiral SFC (Method A): Rt = 6.41 min, 96.19%

Example 31. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 189)



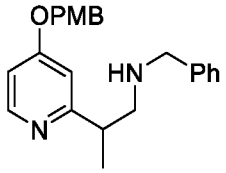
Step 1. 4-((4-Methoxybenzyl)oxy)-2-(prop-1-en-2-yl)pyridine



In a 250 mL two neck round bottom flask under a nitrogen atmosphere, ethanol (150 mL) was added, and the solution was degassed using nitrogen for 15 min. To this solution, 2-chloro-4-((4-methoxybenzyl)oxy)pyridine (9.5 g, 38.0 mmol), potassium isopropenyltrifluoroborate (8.44 g, 57.1 mmol), TEA (5.30 mL, 38.0 mmol) and $PdCl_2$(dppf) (1.392 g, 1.902 mmol) were added at RT. The resulting reaction was stirred at 100 °C for 16 h. The reaction progress was monitored by TLC (50% EtOAc in hexane) and LCMS. The reaction was filtered through a Celite® pad, and the pad was washed with EtOAc (2 x 200 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by silica gel flash column chromatography using EtOAc in hexane

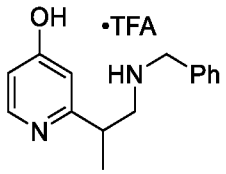
(product eluted in 20% EtOAc in hexane) to obtain 4-((4-methoxybenzyl)oxy)-2-(prop-1-en-2-yl)pyridine (4.8 g, 44.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (d, J = 5.6 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.19 (d, J = 2.1 Hz, 1H), 6.99 – 6.93 (m, 3H), 5.91 (d, J = 0.8 Hz, 1H), 5.30 – 5.26 (m, 1H), 5.14 (s, 2H), 3.77 (s, 3H), 2.11 (s, 3H); LCMS (Method G): Rt = 2.00 min, m/z = 256.2 $[M+H]^+$; 90.96%.

Step 2. (±)-N-Benzyl-2-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)propan-1-amine



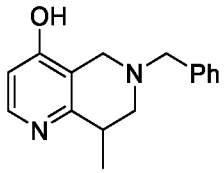
In a pressure vial, 4-((4-methoxybenzyl)oxy)-2-(prop-1-en-2-yl)pyridine (2.5 g, 9.79 mmol) was added in ethanol (20 mL). To this solution, acetic acid (0.560 mL, 9.79 mmol) and benzylamine (2.139 mL, 19.58 mmol) were added. The reaction was stirred at 90 °C for 24 h. The reaction was monitored by TLC (30% EtOAc in hexane). The crude LCMS showed starting material (18%) and desired product mass (21.6%). The reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using 35-40% EtOAc in hexane to recover starting material (1 g) and then, the column was eluted with MeOH in DCM (product eluted at 20% MeOH in DCM) to obtain (±)-*N*-benzyl-2-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)propan-1-amine (1 g, 17.58% yield) as a gummy liquid. LCMS (Method G): Rt = 1.99 min, m/z = 363.3 $[M+H]^+$; 62.40%.

Step 3. (±)-2-(1-(Benzylamino)propan-2-yl)pyridin-4-ol 2,2,2-trifluoroacetic acid



To a stirred solution of (±)-*N*-benzyl-2-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)propan-1-amine (1 g, 2.76 mmol) in DCM (5 mL), TFA (12.07 mL, 157 mmol) was added dropwise at 0 °C under a nitrogen atmosphere. The reaction was allowed to stir at RT for 2 h. The reaction became purple. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude (±)-2-(1-(benzylamino)propan-2-yl)pyridin-4-ol 2,2,2-trifluoroacetic acid (1 g, 40.8% Yield). LCMS (Method F): Rt = 1.26 min, m/z = 243.3 $[M+H]^+$; 56.93%. This material was used without further purification.

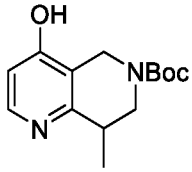
Step 4. (±)-6-Benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



To a stirred solution of (±)-2-(1-(benzylamino)propan-2-yl)pyridin-4-ol 2,2,2-trifluoroacetic acid (490 mg, 1.375 mmol) in MeOH (10 mL), formaldehyde (0.167 mL, 2.063 mmol, 37% aq. solution) was added at 0 °C under nitrogen atmosphere. The reaction was stirred at 70 °C for 48 h, and reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain a crude sticky liquid. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain (±)-6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (250 mg, 68.2% yield) as a solid. LCMS (Method D): Rt = 1.45 min, m/z = 255.1 $[M+H]^+$; 95.45%.

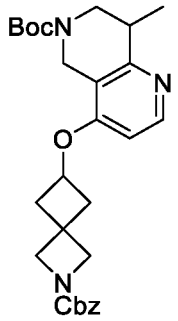
Note: Traces of TFA remained with the product.

Step 5. (±)-tert-Butyl 4-hydroxy-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



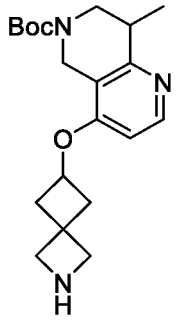
A solution of (±)-6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (250 mg, 0.983 mmol) in dry MeOH (4 mL) was degassed with nitrogen for 2 min. To this solution, Pd-C (118 mg, 0.111 mmol) and $(Boc)_2O$ (0.677 mL, 2.95 mmol) were added at RT under a nitrogen atmosphere. The reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 10 mL). The filtrate was concentrated under reduced pressure to afford (±)-*tert*-butyl 4-hydroxy-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (190 mg, 64.7% yield) as a solid. LCMS (Method G): Rt = 1.25 min, m/z = 265.3$[M+H]^+$; 88.44%.

Step 6. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 10 mL pressure vial, (±)-*tert*-butyl 4-hydroxy-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (190 mg, 0.719 mmol) and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (308 mg, 0.863 mmol) were added in DMF (3 mL). To this reaction mixture, K_2CO_3 (298 mg, 2.156 mmol) was added at RT, and the reaction was stirred at 100 °C for 18 h. The reaction progress was monitored by TLC (50% EtOAc in DCM). The reaction was quenched with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine solution (40 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford the crude product. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were concentrated under reduced pressure to afford (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (120 mg, 33.8% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, J = 5.4 Hz, 1H), 7.40 – 7.30 (m, 5H), 6.72 (d, J = 5.6 Hz, 1H), 5.03 (s, 2H), 4.82 – 4.68 (m, 1H), 4.55 – 4.16 (m, 2H), 4.09 – 3.91 (m, 4H), 3.55 (br s, 2H), 2.95 – 2.84 (m, 1H), 2.83 – 2.73 (m, 2H), 2.30 – 2.22 (m, 2H), 1.43 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H); LCMS (Method G): Rt = 2.18 min, m/z = 494.4 $[M+H]^+$; 99.83%.

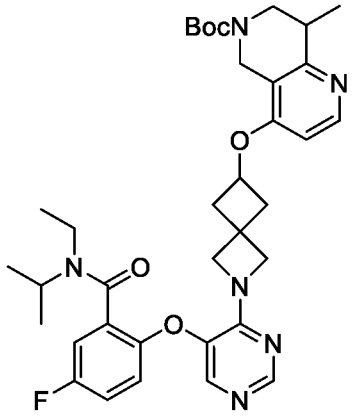
Step 7. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (120 mg, 0.243 mmol) in

2,2,2,-trifluoroethanol (3 mL), Pd-C (80 mg, 0.075 mmol) and acetic acid (1.460 mg, 0.024 mmol) were added at RT. The reaction was stirred at RT for 3 h under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (10% MeOH in DCM). The reaction was bubbled with nitrogen gas for 5 min, filtered through a Celite® pad, and the pad was washed with 2,2,2,-trifluoroethanol (50 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 95% yield) as a sticky liquid. LCMS (Method D): Rt = 1.55 min, m/z = 360.2 $[M+H]^+$; 82.81%. This material was used without further purification.

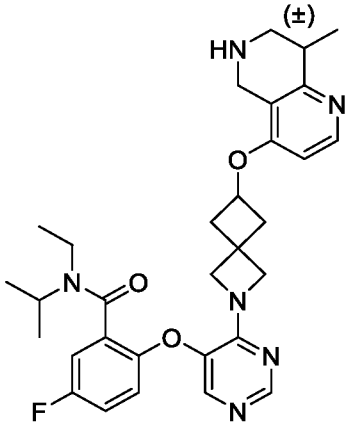
Step 8. (±)-tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (113 mg, 0.334 mmol) in IPA (3 mL), (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.278 mmol) and TEA (0.116 mL, 0.835 mmol) were added at RT under nitrogen atmosphere. The reaction was stirred at 80 °C for 16 h. The reaction progress was monitored by TLC (5% MeOH in DCM). The reaction was diluted with water (20 mL), concentrated under reduced pressure, and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to afford (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 51.4% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.24 (m, 2H), 7.76 – 7.64 (m, 1H), 7.34 – 7.20 (m, 2H), 7.11 – 6.99 (m, 1H), 6.75 – 6.68 (m, 1H), 4.83

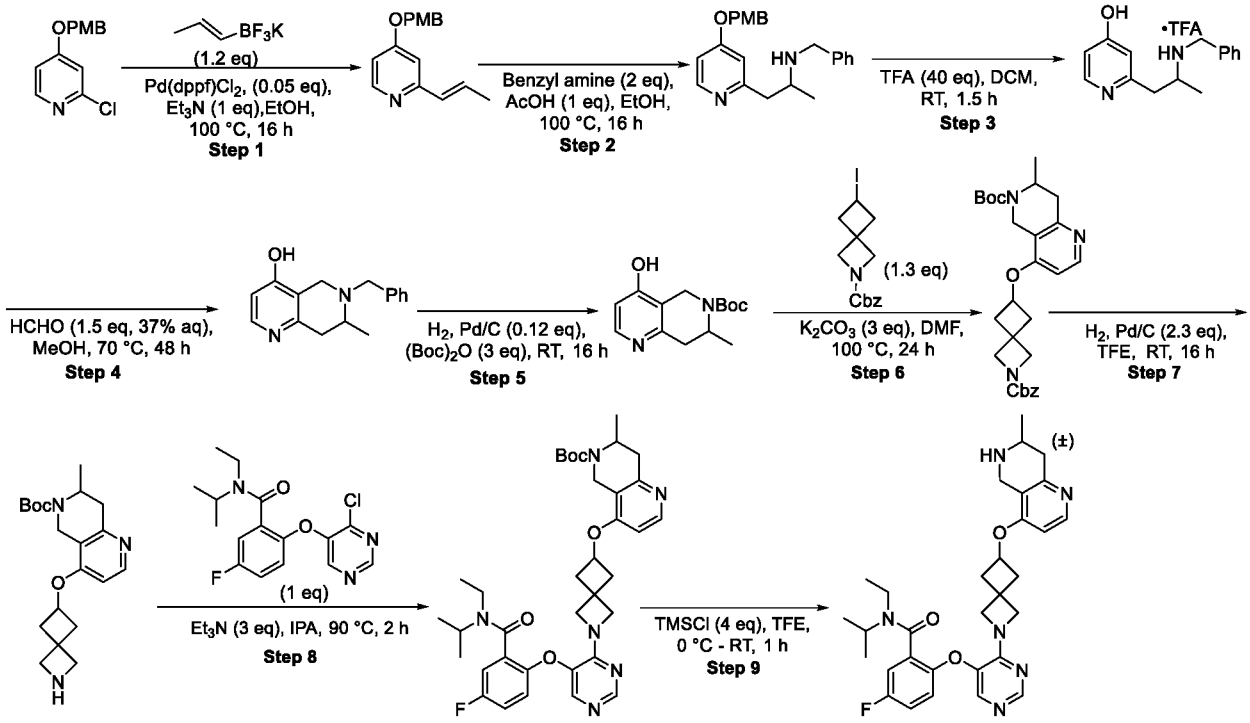
– 4.68 (m, 1H), 4.58 – 4.44 (m, 1H), 4.35 – 4.10 (m, 5H), 3.82 – 3.67 (m, 1H), 3.61 – 3.48 (m, 2H), 3.45 – 3.35 (m, 1H), 3.28 – 3.11 (m, 1H), 2.91 – 2.86 (m, 1H), 2.84 – 2.76 (m, 2H), 2.33 – 2.20 (m, 2H), 1.43 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H), 1.12 – 0.93 (m, 9H); LCMS (Method G): Rt = 2.06 min, m/z = 661.6 $[M+H]^+$; 94.53%.

Step 9. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

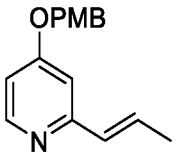


In a 25 mL round bottom flask, (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.151 mmol) was added in TFE (3 mL). To this solution, TMSCl (0.077 mL, 0.605 mmol) was added at 0 °C. The reaction was stirred to RT for 1 h. The reaction progress was monitored by TLC (20% MeOH in DCM). The reaction was concentrated under reduced pressure to afford crude (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain racemic (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (29 mg, 34.11% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 – 8.25 (m, 1H), 8.22 – 8.18 (m, 1H), 7.78 – 7.61 (m, 1H), 7.38 – 7.18 (m, 2H), 7.13 – 6.98 (m, 1H), 6.66 –6.61 (m, 1H), 4.76 – 4.66 (m, 1H), 4.34 – 4.07 (m, 4H), 3.79 – 3.74 (m, 1H), 3.70 (s, 2H), 3.42 – 3.38 (m, 1H), 3.27 – 3.10 (m, 1H), 3.05 (dd, J = 4.8, 12.3 Hz, 1H), 2.80 – 2.69 (m, 4H), 2.66 – 2.61 (m, 1H), 2.25 – 2.20 (m, 2H), 1.22 (d, J = 7.0 Hz, 3H), 1.14 – 0.96 (m, 9H); LCMS (Method B): Rt = 1.05 min, m/z = 561.3 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 99.54%; Chiral SFC (Method AD): Peak 1: Rt = 6.89 min, 50.06%; Peak 2: Rt = 7.93 min, 49.61%.

Example 32. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 180)



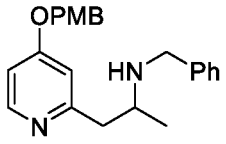
Step 1. (E)-4-((4-Methoxybenzyl)oxy)-2-(prop-1-en-1-yl)pyridine



A 500 mL three neck round bottom flask containing ethanol (200 mL) was degassed by purging with argon gas for 15 min. To this solution, 2-chloro-4-((4-methoxybenzyl)oxy)pyridine (10 g, 40.0 mmol) and potassium (*E*)-trifluoro(prop-1-en-1-yl)borate (7.11 g, 48.1 mmol) were added at RT under argon atmosphere. To this reaction mixture, TEA (5.63 mL, 40.0 mmol) and $PdCl_2$(dppf) (1.465 g, 2.002 mmol) were added, and the reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with EtOAc (3 x 100 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by flash column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain (*E*)-4-((4-methoxybenzyl)oxy)-2-(prop-1-en-1-yl)pyridine (7.3 g, 57.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (d, J = 5.6 Hz, 1H), 7.40 (d, J = 8.6 Hz, 2H),

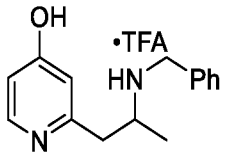
7.01 - 6.93 (m, 4H), 6.86 - 6.82 (m, 1H), 6.46 - 6.40 (m, 1H), 5.13 - 5.07 (m, 2H), 3.76 (s, 3H), 1.87 (dd, J = 1.4, 6.8 Hz, 3H); LCMS (Method G): Rt = 1.96 min, m/z = 256.2 $[M+H]^+$, 80.95%.

Step 2. (±)-N-Benzyl-1-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)propan-2-amine



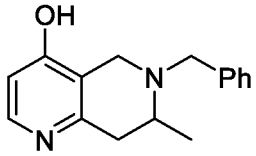
To a stirred solution of (*E*)-4-((4-methoxybenzyl)oxy)-2-(prop-1-en-1-yl)pyridine (1 g, 3.92 mmol) in ethanol (10 mL), benzylamine (0.857 mL, 7.83 mmol) and acetic acid (0.224 mL, 3.92 mmol) were added at RT under nitrogen atmosphere. The reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to RT, and the solvent was evaporated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH and DCM (product was eluted at 5% MeOH in DCM) to obtain (±)-*N*-benzyl-1-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)propan-2-amine (550 mg, 38.2% yield) as a solid. ^{1}H NMR (400 MHz, methanol-d_4): δ 8.27 (d, J = 5.8 Hz, 1H), 7.42 - 7.26 (m, 7H), 6.97 - 6.89 (m, 4H), 5.10 (s, 2H), 3.97 (s, 2H), 3.82 (m, 3H), 3.25 - 3.14 (m, 1H), 3.04 - 2.94 (m, 1H), 2.83 - 2.74 (m, 1H), 1.16 (d, J = 6.4 Hz, 3H), -NH proton was not observed; LCMS (Method G): Rt = 2.01 min, m/z = 363.3 $[M+H]^+$, 98.62%.

Step 3. (±)-2-(2-(Benzylamino)propyl)pyridin-4-ol 2,2,2-trifluoroacetic acid



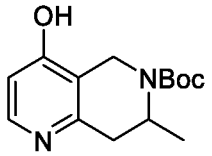
To a stirred solution of (±)-*N*-benzyl-1-(4-((4-methoxybenzyl)oxy)pyridin-2-yl)propan-2-amine (700 mg, 1.931 mmol) in DCM (10 mL), TFA (5.91 mL, 77 mmol) was added slowly over 5 minutes at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (15% MeOH in DCM). After completion, the rection was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH and DCM (product eluted at 20% MeOH in DCM) to obtain (±)-2-(2-(benzylamino)propyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (685 mg, 99% yield) as a semisolid. ^{1}H NMR (400 MHz, methanol-d_4): δ 8.26 – 8.15 (m, 1H), 7.61 – 7.42 (m, 5H), 6.92 – 6.83 (m, 2H), 4.42 – 4.27 (m, 2H), 3.84 – 3.71 (m, 1H), 3.50 – 3.40 (m, 1H), 3.10 – 2.96 (m, 1H), 1.41 (d, J = 6.6 Hz, 3H), -NH and -OH protons were not observed; LCMS (Method G): Rt = 1.16 min, m/z = 243.3 $[M+H]^+$, 99.02%.

Step 4. (±)-6-Benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



To a stirred solution of (±)-2-(2-(benzylamino)propyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (850 mg, 2.385 mmol) in MeOH (25 mL), formaldehyde solution (0.266 mL, 3.58 mmol; 37 wt% in water) was added slowly at RT. The reaction was stirred at 70 °C for 48 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH and DCM (product was eluted at 15% MeOH in DCM) to obtain (±)-6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (500 mg, 79% yield) as a semisolid. ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.78 (d, *J* = 7.3 Hz, 1H), 7.55 – 7.41 (m, 5H), 6.39 (d, *J* = 7.2 Hz, 1H), 4.40 – 4.27 (m, 1H), 4.24 – 4.10 (m, 1H), 3.89 (s, 2H), 3.74 (s, 1H), 3.27 – 3.13 (m, 1H), 2.91 – 2.76 (m, 1H), 1.46 (d, *J* = 6.7 Hz, 3H), -OH proton not observed; LCMS (Method A): Rt = 1.69 min, m/z = 255.2 $[M+H]^+$, 96.36%.

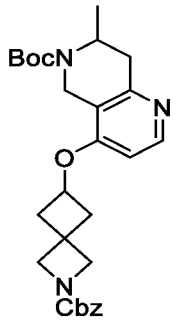
Step 5. (±)-tert-Butyl 4-hydroxy-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 100 mL round bottom flask under an argon atmosphere, (±)-6-benzyl-7methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (450 mg, 1.769 mmol) was dissolved in MeOH (10 mL). To this solution, Pd-C (225 mg, 0.211 mmol) and $(Boc)_2O$ (1.232 mL, 5.31 mmol) were added, and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 35 mL). The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain (±)-*tert*-butyl 4-hydroxy-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (164 mg, 34.5% yield) as a semisolid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.73 (d, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 7.2 Hz, 1H), 4.79 – 4.66 (m, 2H), 4.00 – 3.92 (m, 1H), 3.10 – 2.98 (m, 1H), 2.58 – 2.50 (m, 1H), 1.52 (s,

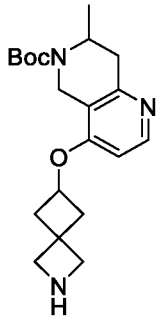
9H), 1.15 (d, *J* = 6.9 Hz, 3H) -OH proton not observed; LCMS (Method F): Rt = 1.39 min, m/z = 265.2 $[M+H]^+$, 98.29%.

Step 6. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



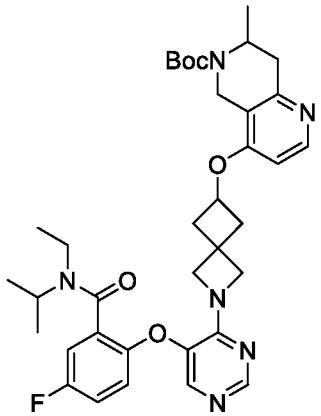
To a stirred solution of (±)-*tert*-butyl 4-hydroxy-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.160 g, 0.605 mmol) in DMF (10 mL), powdered dry K_2CO_3 (0.251 g, 1.816 mmol) was added at RT under nitrogen atmosphere. To this reaction mixture, benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (0.281 g, 0.787 mmol) was added and stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to 0 °C, diluted with ice-cold water (50 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extract was washed with brine solution (2 x 50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 20% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.110 g, 19.88% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, *J* = 5.7 Hz, 1H), 7.38 – 7.31 (m, 5H), 6.74 (d, *J* = 5.7 Hz, 1H), 5.03 (s, 2H), 4.81 – 4.72 (m, 1H), 4.67 – 4.50 (m, 2H), 4.12 – 3.89 (m, 6H), 3.07 – 2.98 (m, 1H), 2.77 – 2.74 (m, 1H), 2.72 – 2.58 (m, 1H), 2.37 – 2.19 (m, 2H), 1.43 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H); LCMS (Method D): Rt = 2.27 min, m/z = 494.3 $[M+H]^+$, 54.42%.

Step 7. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 50 mL round bottom flask under an argon atmosphere, (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (110 mg, 0.223 mmol) was added in 2,2,2-trifluoroethanol (10 mL). To this solution, Pd-C (55 mg, 0.517 mmol) was added, and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (3 x 25 mL). The filtrate was concentrated under reduced pressure to obtain (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (50 mg, 34.1% yield) as a semi-solid. LCMS (Method F): Rt = 1.44 min, m/z = 360.4 $[M+H]^+$, 54.69%.

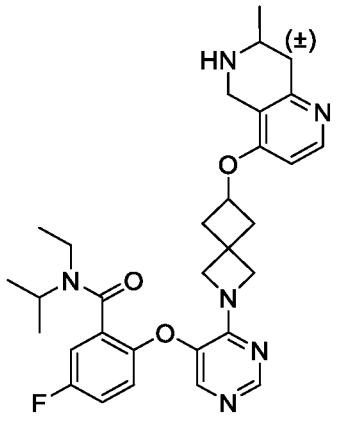
Step 8. (±)-tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (50 mg, 0.139 mmol) in IPA (2 mL), TEA (0.058 mL, 0.417 mmol) was added at RT under nitrogen atmosphere. To this reaction mixture, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (47.0 mg, 0.139 mmol) was added, and the reaction was stirred at 90 °C for 2 h. The progress of the reaction

was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH and DCM (product was eluted at 10% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (44 mg, 45.5% yield)) as a solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.29 – 8.24 (m, 2H), 7.80 – 7.75 (m, 1H), 7.26 – 7.17 (m, 2H), 7.04 – 6.94 (m, 1H), 6.83 – 6.80 (m, 1H), 4.89 – 4.83 (m, 2H), 4.82 – 4.71 (m, 2H), 4.44 – 4.22 (m, 2H), 4.13 (d, *J* = 18.0 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.61 – 3.48 (m, 1H), 3.45 – 3.36 (m, 1H), 3.31 – 3.24 (m, 1H), 3.17 – 3.08 (m, 1H), 2.95 – 2.80 (m, 2H), 2.77 – 2.67 (m, 1H), 2.50 – 2.38 (m, 2H), 1.52 (s, 9H), 1.37 – 1.23 (m, 4H), 1.23 – 1.09 (m, 9H); LCMS Method F): (Rt = 2.30 min, m/z = 661.2 $[M+H]^+$, 95.07%.

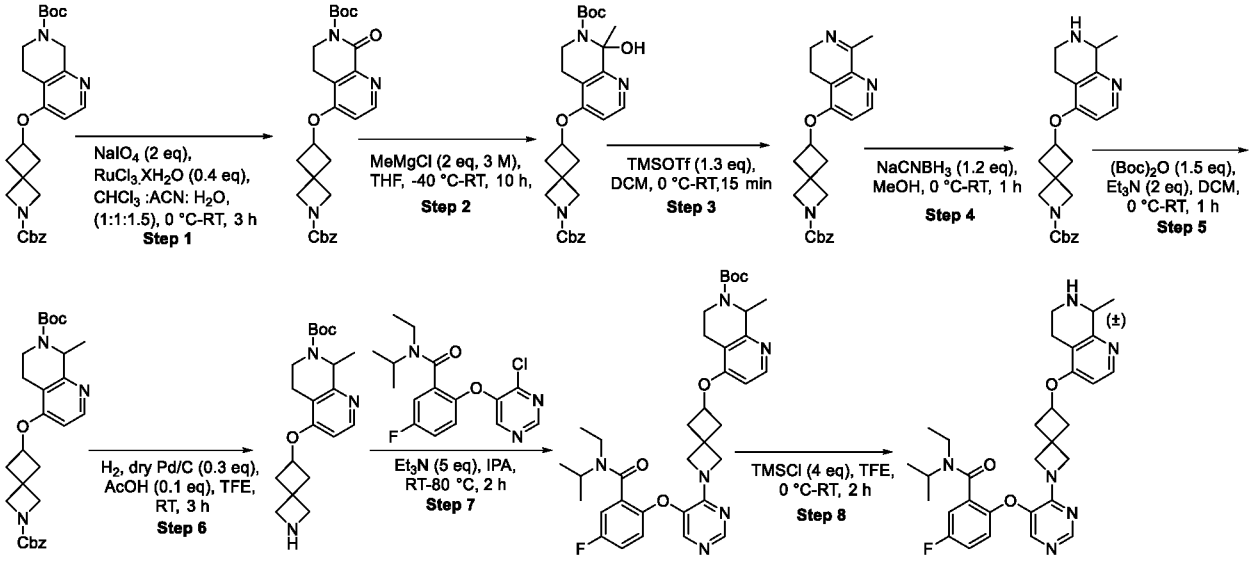
Step 9. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



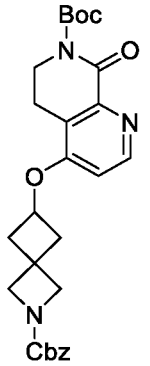
To a stirred solution of (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (40 mg, 0.061 mmol) in 2,2,2-trifluoroethanol (2 mL), TMSCl (0.031 mL, 0.242 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by LCMS (Method G). After completion, the reaction was concentrated under reduced pressure to obtain crude (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (25 mg, 72.3% yield) as a

solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 - 8.26 (m, 1H), 8.16 (d, J = 2.3 Hz, 1H), 7.75 - 7.66 (m, 1H), 7.34 – 7.21 (m, 2H), 7.09 – 6.99 (m, 1H), 6.64 (d, J = 2.9 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.30 – 4.06 (m, 4H), 3.87 (d, J = 16.7 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.62 (d, J = 16.7 Hz, 1H), 3.48 – 3.36 (m, 1H), 3.27 – 3.06 (m, 1H), 2.91 – 2.82 (m, 1H), 2.81 – 2.74 (m, 2H), 2.73 – 2.66 (m, 1H), 2.42 – 2.32 (m, 1H), 2.29 – 2.18 (m, 3H), 1.22 – 0.96 (m, 12H); LCMS (Method G): Rt = 1.69 min, m/z = 561.2 $[M+H]^+$; HPLC (Method A): Rt = 4.67 min, 98.13%.

Example 33. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 209)



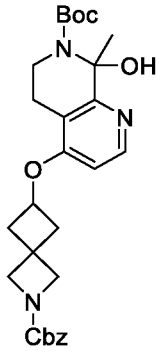
Step 1. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-oxo-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



To a solution of *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (1 g, 2.085 mmol) in chloroform (4 mL), ACN (4 mL) and water (6 mL), $RuCl_3.xH_2O$ (0.173 g, 0.834 mmol) and $NaIO_4$ (0.892 g, 4.17 mmol) were added at 0 °C, and the reaction was stirred at RT for 3 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was diluted with DCM (100 mL) and

filtered through a Celite® pad. The filtrate was washed with brine (30 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford the crude product. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted in 4% MeOH in DCM). The product fractions were concentrated under reduced pressure to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-oxo-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.5 g, 44.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 – 8.28 (m, 1H), 7.42 – 7.30 (m, 5H), 7.06 – 6.76 (m, 1H), 5.03 (s, 2H), 4.86 – 4.72 (m, 1H), 4.09 – 3.83 (m, 6H), 2.89 (t, *J* = 6.1 Hz, 2H), 2.84 – 2.74 (m, 2H), 2.32 – 2.22 (m, 2H), 1.55 – 1.38 (m, 9H); LCMS (Method D): Rt = 2.04 min, m/z = 494.2 $[M+H]^+$; 92.23%.

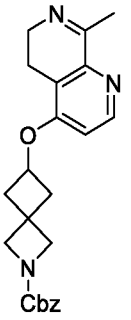
Step 2. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-hydroxy-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



In a 25 mL two neck round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-oxo-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.5 g, 1.013 mmol) was added in THF (9 mL). To this solution, MeMgCl (0.675 mL, 2.026 mmol, 3 M in THF) was added dropwise at -40 °C over 10 min, and the reaction was warmed to RT and stirred for 10 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was quenched with aq. NH_4Cl solution (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine solution (5 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 4% MeOH in DCM). The product fractions were concentrated under reduced pressure to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-hydroxy-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.250 g, 45.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, *J* = 5.5 Hz, 1H), 7.41 – 7.29 (m, 5H), 6.97 (d, *J* = 5.7 Hz, 1H), 5.03 (s, 2H), 4.84 – 4.72 (m, 1H), 4.08 – 3.91 (m, 4H), 3.13 – 3.05 (m, 2H), 2.92 – 2.83 (m, 2H), 2.81

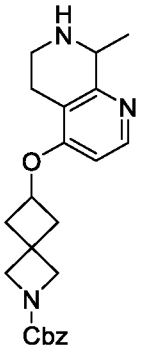
– 2.75 (m, 2H), 2.57 (s, 3H), 2.36 – 2.22 (m, 2H), 1.32 (s, 9H); -OH peak was not observed; LCMS (Method G): Rt = 2.14 min, m/z = 510.5 $[M+H]^+$; 94.74%.

Step 3. Benzyl 6-((8-methyl-5,6-dihydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-hydroxy-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.250 g, 0.491 mmol) in DCM (3 mL), TMSOTf (0.116 mL, 0.638 mmol) was added at 0 °C. The reaction was stirred for 15 min at RT. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was quenched with water (5 mL) and extracted with 10% MeOH in DCM (2 x 10 mL). The combined organic layer was washed with brine solution (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain the crude benzyl 6-((8-methyl-5,6-dihydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate) as a solid (250 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 – 8.09 (m, 1H), 7.42 – 7.28 (m, 5H), 6.95 – 6.84 (m, 1H), 5.03 (s, 2H), 4.85 – 4.63 (m, 1H), 4.10 – 3.86 (m, 4H), 3.61 – 3.52 (m, 2H), 2.82 – 2.72 (m, 2H), 2.66 – 2.61 (m, 1H), 2.31 – 2.22 (m, 3H), 1.84 (s, 3H); LCMS (Method G): Rt = 1.74 min, m/z = 392.3 $[M+H]^+$; 97.57%. This material was used without further purification.

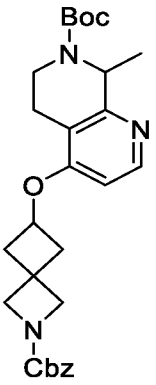
Step 4. (±)-Benzyl 6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



In a 25 mL two neck round bottom flask under nitrogen atmosphere, benzyl 6-((8-methyl-5,6-dihydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.250

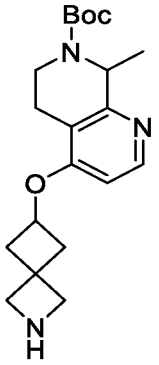
g, 0.639 mmol) was added in MeOH (1 mL). To this solution, $NaCNBH_3$ (0.048 g, 0.766 mmol) was added at 0 °C, and the reaction was allowed to stir at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was quenched with water (5 mL) and extracted with 10% MeOH in DCM (2 x 15 mL). The combined organic layer was washed with brine solution (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain (±)-benzyl 6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (220 mg, 88% yield) as a solid. LCMS (Method D): Rt = 1.74 min, m/z = 394.2 $[M+H]^+$; 97.80%.

Step 5. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



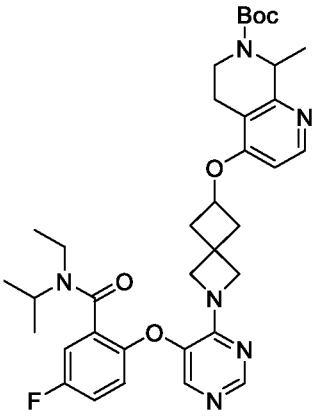
In a 25 mL two neck round bottom flask under nitrogen atmosphere, (±)-benzyl 6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.22 g, 0.559 mmol) was added in DCM (1 mL). To this solution, TEA (0.152 mL, 1.118 mmol) and $(Boc)_2O$ (0.191 mL, 0.839 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was quenched with water (10 mL) and extracted with 10% MeOH in DCM (2 x 20 mL). The combined organic layer was washed with brine solution (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (260 mg, 80% yield) as a solid. LCMS (Method D): Rt = 2.36 min, m/z = 494.2 $[M+H]^+$; 85.47%.

Step 6. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.260 g, 0.527 mmol) in TFE (3 mL), AcOH (3.01 µL, 0.053 mmol) and dry Pd/C (0.168 g, 0.158 mmol) were added at RT. The reaction was stirred for 3 h at RT under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (10% MeOH in DCM). The reaction was diluted with MeOH (50 mL), filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (220 mg, 43.0% yield) as a gummy solid. LCMS (Method D): Rt = 1.60 min, m/z = 360.2 $[M+H]^+$; 43.06%. This material was used without further purification.

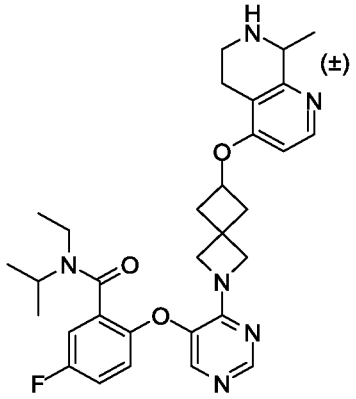
Step 7. (±)-tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



To a stirred solution of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.220 g, 0.651 mmol) in dry IPA (2 mL), TEA (0.444 mL, 3.26 mmol) was added at RT under nitrogen atmosphere, and the solution was stirred for 5 min. To this solution, (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.234 g, 0.651 mmol) was added at RT. The reaction was

stirred at 80 °C for 2 h. The reaction progress was monitored by TLC (6% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude compound. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 11% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (60 mg, 12.50% yield) as a solid. LCMS (Method D): Rt = 2.25 min, m/z = 661.4 $[M+H]^+$; 89.66%.

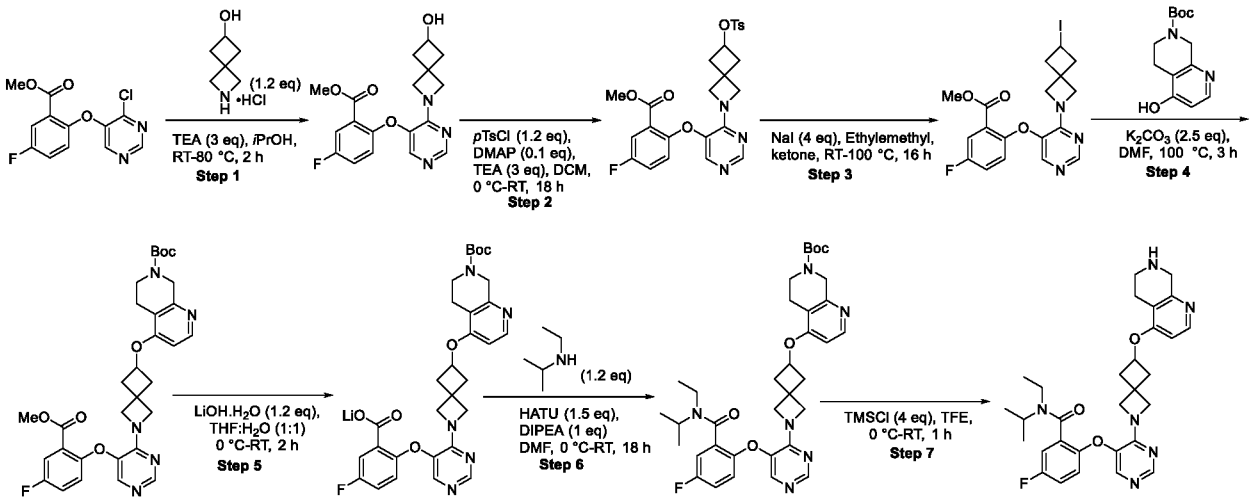
Step 8. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



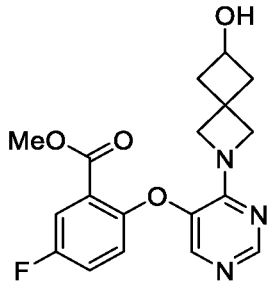
In a 25 mL round bottom flask, (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (0.06 g, 0.091 mmol) was added in TFE (1 mL). To this stirred solution, TMSCl (0.046 mL, 0.363 mmol) was added at 0 °C, and the reaction was stirred at RT for 2 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to afford crude (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were concentrated under reduced pressure and lyophilized to afford (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (25mg, 49.1% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 – 8.26 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 – 7.65 (m, 1H), 7.34 – 7.21 (m, 2H), 7.10 – 7.00 (m, 1H), 6.64 (d, J = 5.5 Hz, 1H), 4.79 – 4.70 (m, 1H), 4.43 – 4.08 (m, 4H), 3.87 – 3.71 (m, 2H), 3.45 – 3.42 (m, 1H), 3.27 – 3.02 (m, 3H), 2.83 – 2.73 (m, 3H), 2.30 – 2.17 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H), 1.22 – 0.98 (m, 9H), two protons merged in solvent peak. LCMS

(Method G): Rt = 1.59 min, m/z = 561.5 $[M+H]^+$; HPLC (Method A): Rt = 4.87 min, 99.92%; Chiral SFC (Method AG): Peak 1: Rt = 7.11 min, 44.75%; Peak 2: Rt = 7.76 min, 54.48%.

Example 34. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 91)

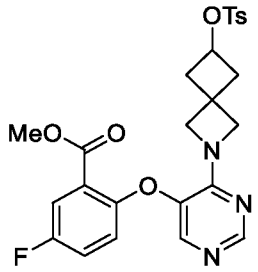


Step 1. Methyl 5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate



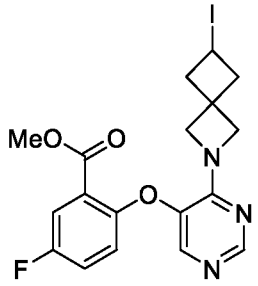
In a 20 mL of pressure vial, methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate (0.500 g, 1.769 mmol) and 2-azaspiro[3.3]heptan-6-ol hydrochloride (0.318 g, 2.123 mmol) were added in 2-propanol (5 mL). To this solution, Et_3N (0.740 mL, 5.31 mmol) was added, and the reaction was stirred at 80 °C for 2 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude methyl 5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (0.298 g, 32.6% yield) as a solid. LCMS (Method G): Rt = 1.53 min, m/z = 360.1 $[M+H]^+$; 69.45%. This material was used without further purification.

Step 2. Methyl 5-fluoro-2-((4-(6-(tosyloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate



In a dried, 100 mL round bottom flask under nitrogen atmosphere, methyl 5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (298 mg, 0.829 mmol) was added in DCM (10 mL). To this solution, TEA (0.347 mL, 2.488 mmol) and DMAP (10.13 mg, 0.083 mmol) were added at 0 °C, and the reaction was stirred for 5 min. To this reaction mixture, *p*TsCl (190 mg, 0.995 mmol) was added at 0 °C, and the reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (100% EtOAc in hexane). The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 13% MeOH in DCM) to obtain methyl 5-fluoro-2-((4-(6-(tosyloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (204 mg, 46.7% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 3.2, 8.8 Hz, 1H), 7.63 (s, 1H), 7.52 – 7.41 (m, 3H), 7.07 (dd, J = 4.5, 9.1 Hz, 1H), 4.79 – 4.72 (m, 1H), 4.17 – 4.07 (m, 4H), 3.79 (s, 3H), 2.42 (s, 3H), 2.35 – 2.23 (m, 2H) two protons merged with solvent peak; LCMS (Method B): Rt = 2.34 min, m/z = 514.0 $[M+H]^+$; 97.40%.

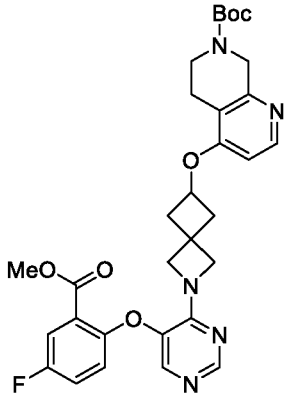
Step 3. Methyl 5-fluoro-2-((4-(6-iodo-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate



In a 50 mL round bottom flask, methyl 5-fluoro-2-((4-(6-(tosyloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (2.0 g, 3.89 mmol) was added in ethyl methyl ketone (30 mL). To this stirred solution, sodium iodide (2.335 g, 15.58 mmol) was added at RT, and the reaction was stirred at 100 °C for 16 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford a crude sticky

liquid. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80-90% EtOAc in hexane) to obtain methyl 5-fluoro-2-((4-(6-iodo-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (870 mg, 36.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 7.69 – 7.63 (m, 2H), 7.48 (ddd, J = 3.2, 7.9, 9.0 Hz, 1H), 7.13 (dd, J = 4.5, 9.1 Hz, 1H), 4.47 (quin, J = 7.8 Hz, 1H), 4.22 (s, 4H), 3.81 (s, 3H), 3.03 – 2.92 (m, 2H), 2.77 – 2.64 (m, 2H); LCMS (Method G): Rt = 1.90 min, m/z = 470.1 $[M+H]^+$; 77.44%.

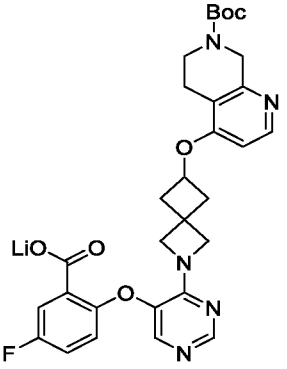
Step 4. tert-Butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



In a 20 mL pressure-released glass vial, methyl 5-fluoro-2-((4-(6-iodo-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoate (400 mg, 0.852 mmol) was added in DMF (5 mL). To this solution, *tert*-butyl 4-hydroxy-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (213 mg, 0.852 mmol) and K_2CO_3 (295 mg, 2.131 mmol) were added at RT. The reaction was stirred at 100 °C for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with cold water (3 x 25 mL) and brine solution (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude product. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 3% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (110 mg, 21.19% yield) as a sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.22 (d, J = 5.5 Hz, 1H), 7.68 (s, 1H), 7.70 – 7.66 (m, 1H), 7.49 (ddd, J = 3.3, 7.8, 9.0 Hz, 1H), 7.10 (dd, J = 4.4, 9.1 Hz, 1H), 6.73 (d, J = 5.8 Hz, 1H), 4.81 – 4.72 (m, 1H), 4.44 (s, 2H), 4.27 (s, 2H), 4.18 (s, 2H), 3.82 (s, 3H), 3.55 (t, J = 5.8 Hz,

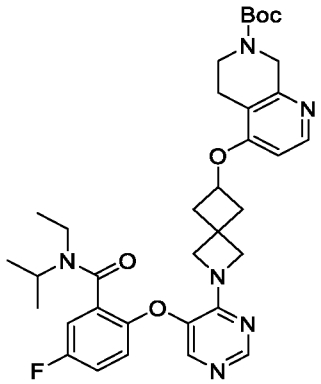
2H), 2.84 – 2.78 (m, 2H), 2.59 (t, *J* = 5.8 Hz, 2H), 2.37 – 2.23 (m, 2H), 1.43 (s, 9H); LCMS (Method G): Rt = 2.15 min, m/z = 592.3 $[M+H]^+$; 97.15%.

Step 5. Lithium 2-((4-(6-((7-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate



In a 50 mL round bottom flask, *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (100 mg, 0.169 mmol) was added in THF (2 mL) and water (2 mL). To this solution, $LiOH.H_2O$ (8.51 mg, 0.203 mmol) was added at 0 °C, and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain crude lithium 2-((4-(6-((7-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate (100 mg, 81% yield) as a sticky solid. LCMS (Method B): Rt = 1.82 min, m/z = 578.0 $[M+H]^+$; 80.15%. This material was used without further purification.

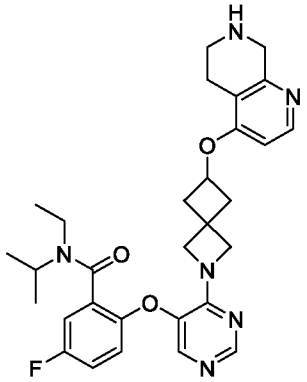
Step 6. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



In a 50 mL round bottom flask, lithium 2-((4-(6-((7-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate (100 mg, 0.171 mmol) was added in DMF (5 mL). To this stirred solution, *N*-

ethylpropan-2-amine (17.92 mg, 0.206 mmol), HATU (98 mg, 0.257 mmol), and DIPEA (0.030 mL, 0.171 mmol) were added at 0 °C. The reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with cold water (4 x 20 mL) and brine solution (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude product. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (104 mg, 80% yield) as a sticky solid. LCMS (Method G): Rt = 2.11 min, m/z = 647.4 $[M+H]^+$; 85.76%.

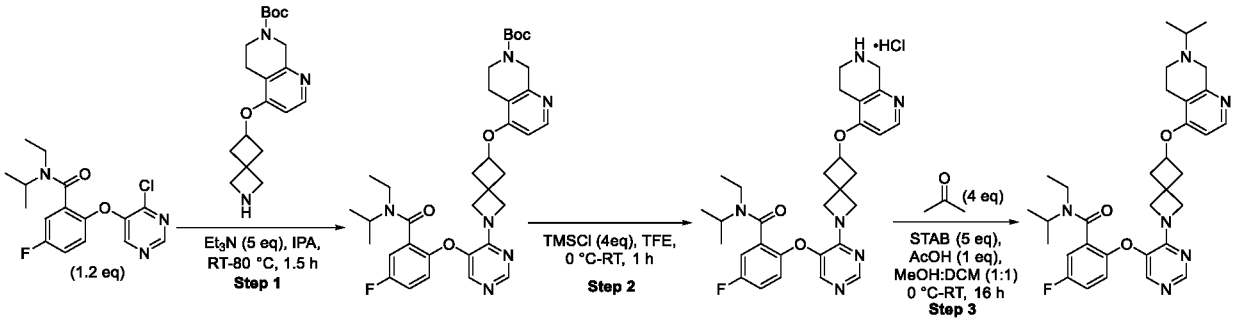
Step 7. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



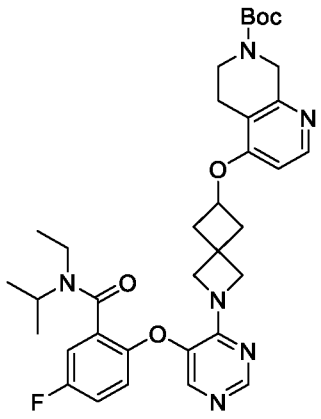
In a 50 mL round bottom flask, *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (100 mg, 0.155 mmol) was added in 2,2,2-trifluoroethanol (3 mL). To this stirred solution, TMSCl (0.079 mL, 0.618 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (100 mg). The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (20.54 mg, 24.29% yield) as a solid. ^{1}H NMR (400 MHz,

DMSO-d_6): δ 8.30 – 8.26 (m, 1H), 8.13 (d, J = 5.6 Hz, 1H), 7.78 – 7.65 (m, 1H), 7.36 – 7.16 (m, 2H), 7.12 – 6.97 (m, 1H), 6.68 – 6.61 (m, 1H), 4.79 – 4.67 (m, 1H), 4.45 – 4.04 (m, 5H), 3.81 – 3.68 (m, 3H), 3.46 – 3.37 (m, 1H), 3.28 – 3.18 (m, 2H), 2.90 (t, J = 5.8 Hz, 2H), 2.84 – 2.74 (m, 2H), 2.27 – 2.20 (m, 2H), 1.22 – 1.00 (m, 9H); One proton is merged with solvent peaks; LCMS (Method G): Rt = 1.73 min, m/z = 547.3 $[M+H]^+$; HPLC (Method A): Rt = 5.05 min, 99.95%.

Example 35. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 208)



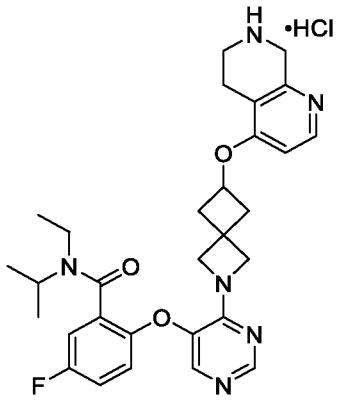
Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



In a 100 mL round bottom flask under nitrogen atmosphere, *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (2.1 g, 6.08 mmol) was added in IPA (15 mL). To this stirred solution, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (2.464 g, 7.29 mmol) and TEA (4.24 mL, 30.4 mmol) were added at RT. The reaction was stirred at 80 °C for 1.5 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude product. To this crude product, water (50 mL) was added and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under

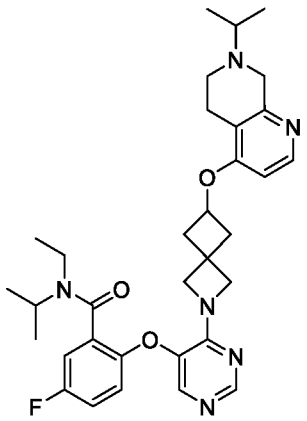
reduced pressure to afford a crude sticky liquid. The crude product was purified by silica gel flash column chromatography using 0-100% EtOAc in hexane and followed by MeOH in DCM (product eluted at 12% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (3.25 g, 78% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.27 (m, 1H), 8.24 – 8.20 (m, 1H), 7.78 – 7.67 (m, 1H), 7.33 – 7.21 (m, 2H), 7.11 – 6.96 (m, 1H), 6.75 – 6.70 (m, 1H), 4.81 – 4.70 (m, 1H), 4.45 (s, 2H), 4.30 – 4.07 (m, 4H), 3.80 – 3.70 (m, 1H), 3.56 (t, J = 5.5 Hz, 2H), 3.45 – 3.35 (m, 1H), 3.29 – 3.11 (m, 1H), 2.83 – 2.74 (m, 2H), 2.61 (t, J = 5.8 Hz, 2H), 2.31 – 2.20 (m, 2H), 1.43 (s, 9H), 1.24 – 0.96 (m, 9H); LCMS (Method G): Rt = 2.11 min, m/z = 647.6 $[M+H]^+$; 94.35%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride



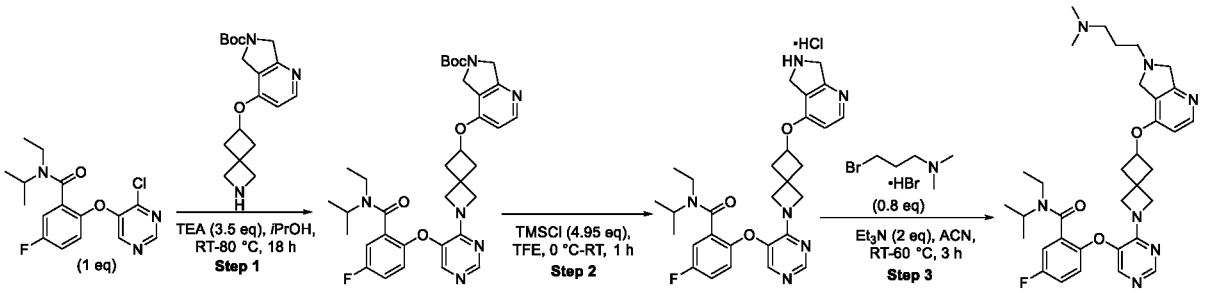
In a 250 mL round bottom flask, *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate (3.2 g, 4.95 mmol) was added in 2,2,2-trifluoroethanol (20 mL). To this solution, TMSCl (2.51 mL, 19.79 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure and co-distilled with EtOAc (3 x 30 mL), and the solid was dried under vacuum to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (2.8 g, 97% yield) as a solid. LCMS (Method C): Rt = 1.69 min, m/z = 547.3 $[M+H]^+$; 90.24%. This material was used without further purification.

Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

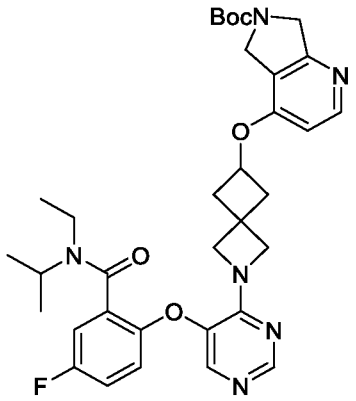


In a 25 mL round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (200 mg, 0.343 mmol) was added in DCM (5 mL). To this solution, TEA (0.048 mL, 0.343 mmol) was added, and the reaction was stirred for 30 min. The reaction was concentrated under reduced pressure, and the residue was dissolved in MeOH (5 mL). To this solution, acetone (0.101 mL, 1.372 mmol) and acetic acid (0.020 mL, 0.343 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (363 mg, 1.715 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (10 mL) and extracted with 10% MeOH in DCM (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude compound. The crude was purified by Prep HPLC (Method C) and pure fractions were concentrated under reduced pressure and lyophilized to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (44.8 mg, 21.86% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 – 8.26 (m, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.78 – 7.62 (m, 1H), 7.33 – 7.20 (m, 2H), 7.11 – 6.99 (m, 1H), 6.69 – 6.63 (m, 1H), 4.80 – 4.71 (m, 1H), 4.45 – 4.09 (m, 4H), 3.83 – 3.66 (m, 1H), 3.57 (s, 2H), 3.46 – 3.36 (m, 1H), 3.27 – 3.14 (m, 1H), 2.89 – 2.74 (m, 3H), 2.71 – 2.63 (m, 2H), 2.59 – 2.55 (m, 2H), 2.28 – 2.21 (m, 2H), 1.24 – 0.98 (m, 15H); LCMS (Method G): Rt = 1.83 min, m/z = 589.6 $[M+H]^+$; HPLC (Method A): Rt = 5.49 min, 99.63%.

Example 36. 2-((4-(6-((6-(3-(Dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 45)

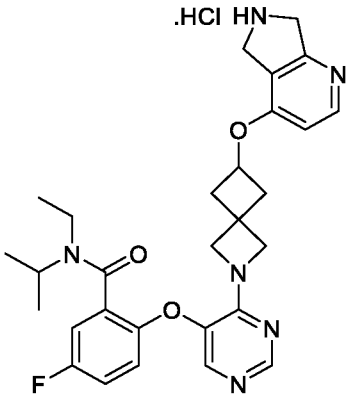


Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



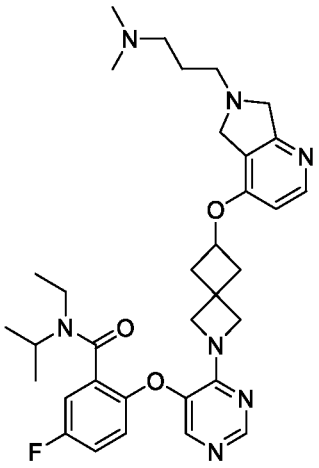
In a 25 mL round bottom flask under nitrogen atmosphere, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (350 mg, 1.036 mmol) and *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (343 mg, 1.036 mmol) were added in 2-propanol (10 mL). To this reaction mixture, TEA (0.505 mL, 3.63 mmol) was added at RT, and the reaction was stirred at 80 °C for 18 h. The reaction was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (500 mg, 69.2% yield) as a sticky liquid. LCMS (Method B): Rt = 2.10 min, m/z = 633.4 $[M+H]^+$; 90.77%.

Step 2. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



In a 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (500 mg, 0.790 mmol) was added in 2,2,2-trifluoroethanol (10 mL). To this solution, TMSCl (0.5 mL, 3.91 mmol) was added at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure to obtain the crude product. The crude product was triturated with EtOAc (5 mL) and filtered, and the solid was dried under reduced pressure to obtain 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (490 mg, quantitative yield). LCMS (Method B): Rt = 1.51 min, m/z = 533.3 $[M+H]^+$; 92.24%.

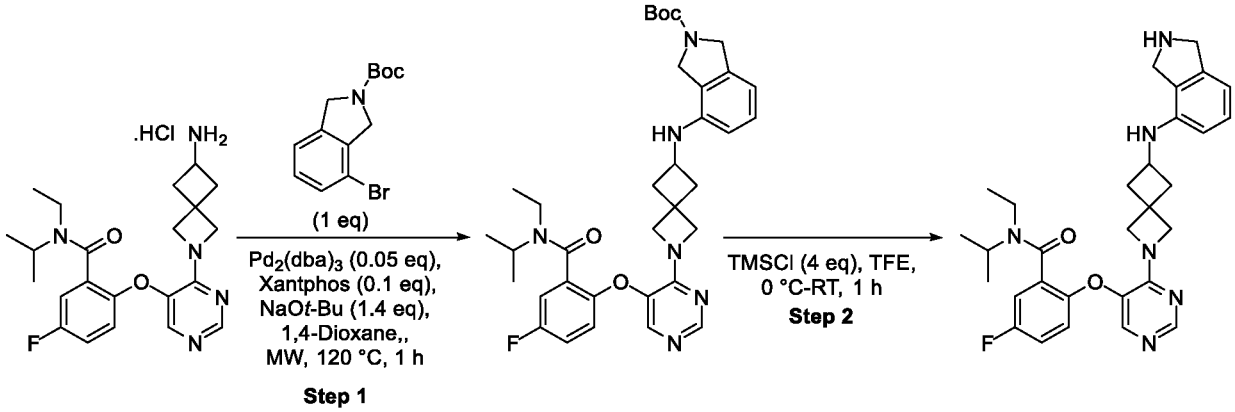
Step 3. 2-((4-(6-((6-(3-(Dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



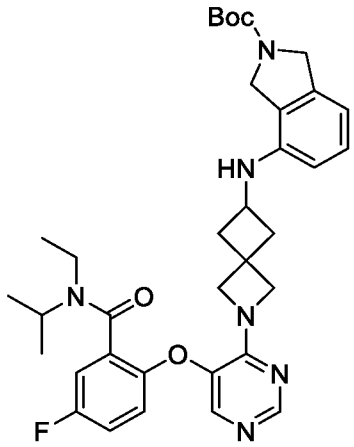
To a solution of 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (250 mg, 0.439 mmol) and 3-bromo-*N*,*N*-dimethylpropan-1-amine

hydrobromide (87 mg, 0.351 mmol) in acetonitrile (6 mL), TEA (0.122 mL, 0.879 mmol) was added at RT. The reaction was stirred at 60 °C for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude product. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the impure product (26 mg, HPLC-89%). The impure product was re-purified by Prep HPLC (Method D) to obtain 2-((4-(6-((6-(3-(dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide (10.74 mg, 3.92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 – 8.28 (m, 1H), 8.23 – 8.16 (m, 1H), 7.78 – 7.64 (m, 1H), 7.33 – 7.21 (m, 2H), 7.11 – 6.99 (m, 1H), 6.76 – 6.66 (m, 1H), 4.83 – 4.73 (m, 1H), 4.46 – 4.05 (m, 4H), 3.81 – 3.70 (m, 4H), 3.45 – 3.39 (m, 1H), 3.28 – 3.06 (m, 2H), 2.85 – 2.72 (m, 2H), 2.70 – 2.64 (m, 2H), 2.31 – 2.18 (m, 4H), 2.12 (s, 6H), 1.61 (quin, J = 7.2 Hz, 2H), 1.22 – 0.95 (m, 9H); LCMS (Method D): Rt = 1.72 min, m/z = 618.4 $[M+H]^+$; HPLC (Method A): Rt = 4.85 min, 99.18%.

Example 37. *N*-Ethyl-5-fluoro-2-((4-(6-(isoindolin-4-ylamino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide (Compound No. 20)

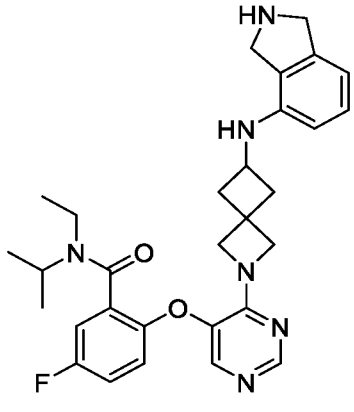


Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)amino)isoindoline-2-carboxylate



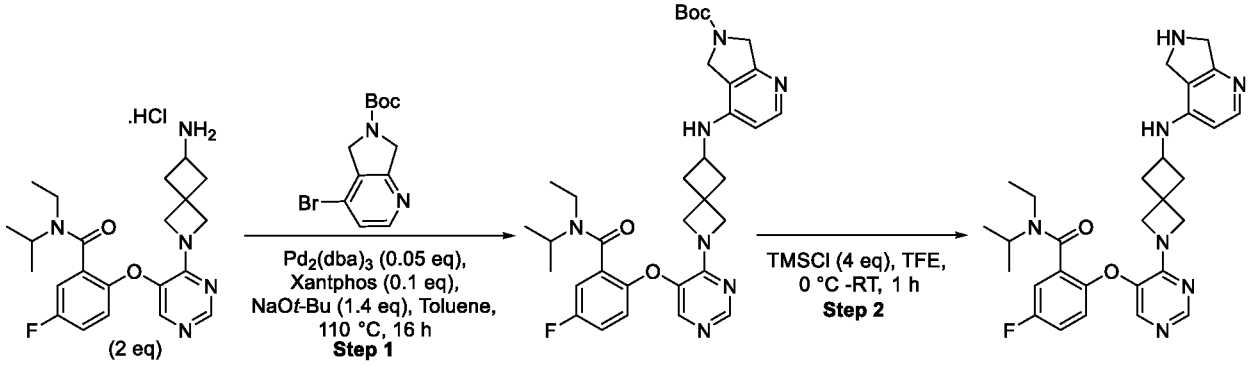
A 30 mL microwave vial containing 1,4-dioxane (10 mL) was degassed by purging with argon gas for 10 min. To this solution, *tert*-butyl 4-bromoisoindoline-2-carboxylate (200 mg, 0.671 mmol)), 2-((4-(6-amino-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (301 mg, 0.671 mmol), and Xantphos (38.8 mg, 0.067 mmol) were added at RT. To this reaction mixture, $Pd_2(dba)_3$ (30.7 mg, 0.034 mmol), and sodium *tert*-butoxide (90 mg, 0.939 mmol) were added under an argon atmosphere. The reaction was irradiated at 120 °C under the microwave for 1 h. The progress of the reaction was monitored by LCMS (Method D). After completion, the reaction was cooled to RT, diluted with water (25 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)amino)isoindoline-2-carboxylate (300 mg, 70.9% yield) as semisolid. LCMS (Method D): Rt = 2.30 min, m/z = 631.3 $[M+H]^+$, 72.87%.

Step 2. *N*-Ethyl-5-fluoro-2-((4-(6-(isoindolin-4-ylamino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide

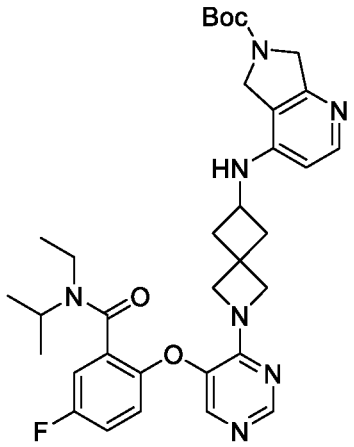


To a stirred solution of *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)amino)isoindoline-2-carboxylate (300 mg, 0.476 mmol) in 2,2,2-trifluoroethanol (5 mL), TMSCl (0.241 mL, 1.902 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by LCMS (Method D). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-ylamino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride. The crude was purified by Prep HPLC (Method L) to obtain *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-ylamino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (25 mg, 9.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 – 8.26 (m, 1H), 7.75 – 7.67 (m, 1H), 7.26 – 7.14 (m, 2H), 7.05 – 6.90 (m, 2H), 6.51 (d, J = 7.3 Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 4.92 – 4.82 (m, 1H), 4.49 – 3.87 (m, 8H), 3.87 – 3.69 (m, 2H), 3.37 – 3.30 (m, 2H), 2.72 – 2.59 (m, 3H), 2.20 – 2.00 (m, 2H), 1.25 – 1.05 (m, 9H); LCMS (Method D): Rt = 1.75 min, m/z = 531.2 $[M+H]^+$; HPLC (Method A): Rt = 4.95 min, 97.76%.

Example 38. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 13)

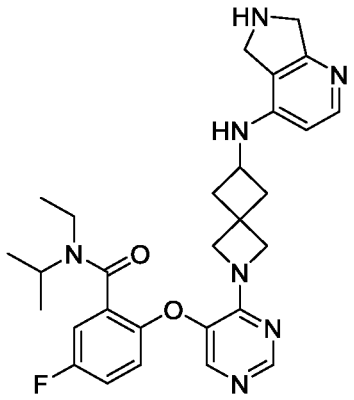


Step 1. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)amino)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



A 25 mL round bottom flask containing toluene (5 mL) was degassed by purging with argon gas for 5-10 min. To this solution, *tert*-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (100 mg, 0.334 mmol), 2-((4-(6-amino-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (276 mg, 0.615 mmol) and Xantphos (19.34 mg, 0.033 mmol) were added. To this reaction mixture, $Pd_2(dba)_3$ (15.30 mg, 0.017 mmol) and potassium *tert*-butoxide (52.5 mg, 0.468 mmol) were added at RT under an argon atmosphere. The reaction was stirred at 110 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 10% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)amino)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (240 mg, 44.1% yield) as a semi-solid. LCMS (Method D): Rt = 1.99 min, m/z = 632.5 $[M+H]^+$, 38.83%.

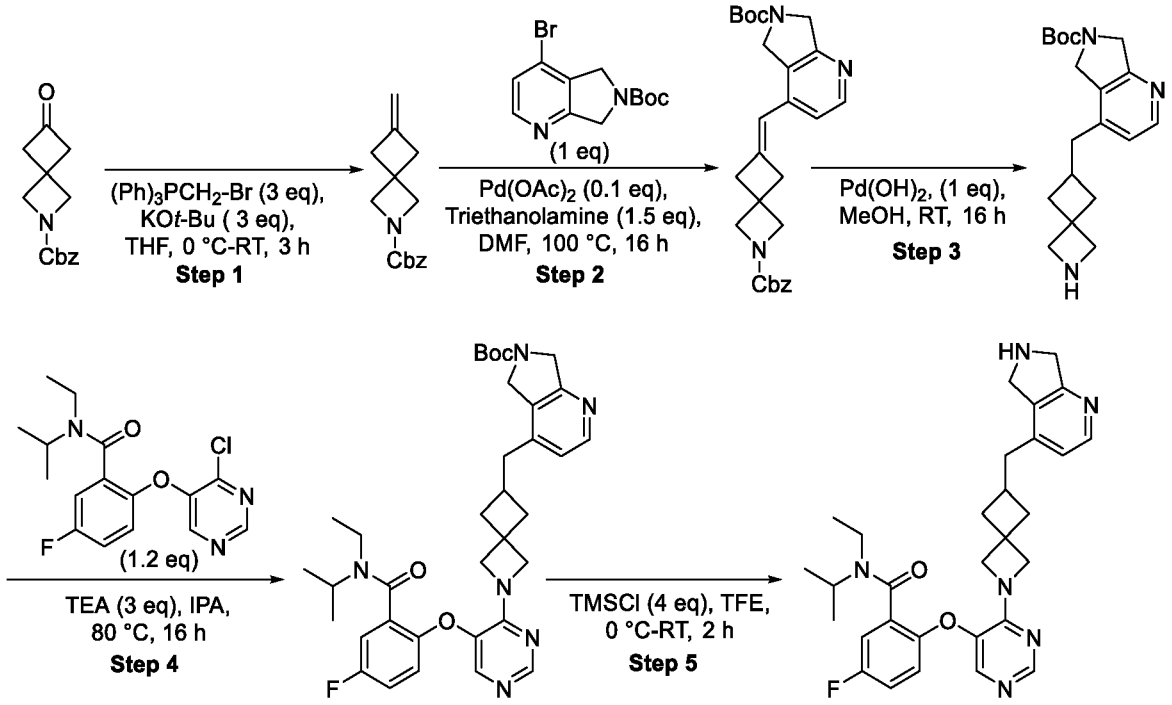
Step 2. 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



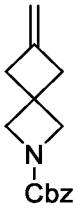
To a stirred solution of *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)amino)-5,7-dihydro-6H-

pyrrolo[3,4-b]pyridine-6-carboxylate (240 mg, 0.380 mmol) in 2,2,2-trifluoroethanol (3 mL), TMSCl (0.194 mL, 1.520 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by LCMS (Method D). After completion, the reaction was concentrated under reduced pressure to obtain crude 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude was purified by Prep HPLC (Method A) to obtain 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (17.01 mg, 8.22% yield) as a solid. ^{1}H NMR (400 MHz DMSO-*d*$_6$): δ 8.29 – 8.26 (m, 1H), 8.00 – 7.89 (m, 1H), 7.75 – 7.68 (m, 1H), 7.38 – 7.19 (m, 2H), 7.06 – 6.96 (m, 1H), 6.22 – 6.10 (m, 2H), 4.46 – 4.38 (m, 1H), 4.34 – 4.10 (m, 3H), 4.08 – 4.00 (m, 1H), 3.96 – 3.69 (m, 5H), 3.47 – 3.37 (m, 1H), 3.27 – 3.09 (m, 2H), 2.65 – 2.58 (m, 2H), 2.21 – 2.09 (m, 2H), 1.29 – 0.99 (m, 9H); LCMS (Method D): Rt = 1.48 min, m/z = 532.2 $[M+H]^+$; HPLC (Method A): Rt = 4.36 min, 97.59%.

Example 39. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 17)

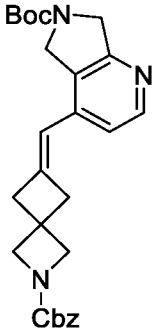


Step 1. Benzyl 6-methylene-2-azaspiro[3.3]heptane-2-carboxylate



To a solution of methyltriphenylphosphonium bromide (2.185 g, 6.12 mmol) in THF (20 mL), potassium *tert*-butoxide (0.686 g, 6.12 mmol) was added at 0 °C under a nitrogen atmosphere, and the reaction was stirred at RT for 1 h. To this reaction mixture, benzyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (0.500 g, 2.039 mmol) in THF (10 mL) was added slowly, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (20% EtOAc in hexane). After completion, the reaction was diluted with cold water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 2-5% EtOAc in hexane) to obtain benzyl 6-methylene-2-azaspiro[3.3]heptane-2-carboxylate (370 mg, 55.2% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 – 7.27 (m, 5H), 5.02 (s, 2H), 4.81 – 4.76 (m, 2H), 3.96 (s, 4H), 2.85 (t, J = 2.4 Hz, 4H); LCMS (Method H): Rt = 2.02 min, m/z = 244.0 $[M+H]^+$, 78.77%.

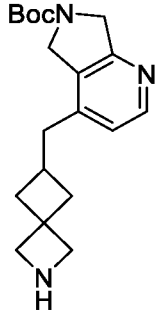
Step 2. *tert*-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-ylidene)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



To a stirred solution of benzyl 6-methylene-2-azaspiro[3.3]heptane-2-carboxylate (350 mg, 1.439 mmol) and *tert*-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (430 mg, 1.439 mmol) in DMF (10 mL), triethanolamine (0.286 mL, 2.158 mmol) and palladium(II) acetate (32.3 mg, 0.144 mmol) were added at RT under nitrogen atmosphere. The reaction was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to RT, diluted with water (25 mL), and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed

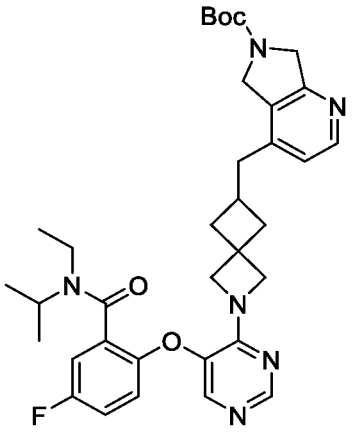
with brine solution (30 mL), dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 50% EtOAc in hexane) to obtain *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-ylidene)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (60 mg, 7.68% yield) as a liquid. LCMS (Method H): Rt = 2.12 min, m/z = 462.2 $[M+H]^+$, 82.68%.

Step 3. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



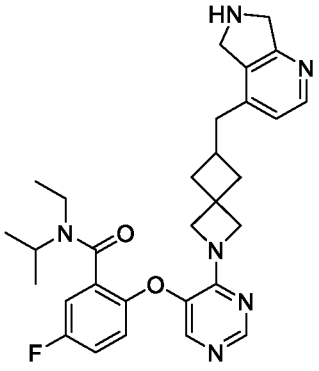
In a 100 mL single neck round bottom flask under an argon atmosphere, *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-ylidene)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (60 mg, 0.13 mmol) was dissolved in MeOH (5 mL). To this solution, $Pd(OH)_2$ (18.26 mg, 0.13 mmol) was added, and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure to obtain *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (60 mg, quantitative yield). The material was used for the next reaction without further purification.

Step 4. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



To a solution of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (90 mg, crude, 0.273 mmol) in IPA (5 mL), TEA (0.118 mL, 0.820 mmol) was added at RT under nitrogen atmosphere. To this reaction mixture, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (111 mg, 0.328 mmol) was added, and the reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and the residue was diluted with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine solution (25 mL), dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude compound. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5-10% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)methyl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (30 mg, 15.84% yield) as semi-solid. LCMS (Method D): Rt = 2.22 min, m/z = 631.3 $[M+H]^+$, 91.11%.

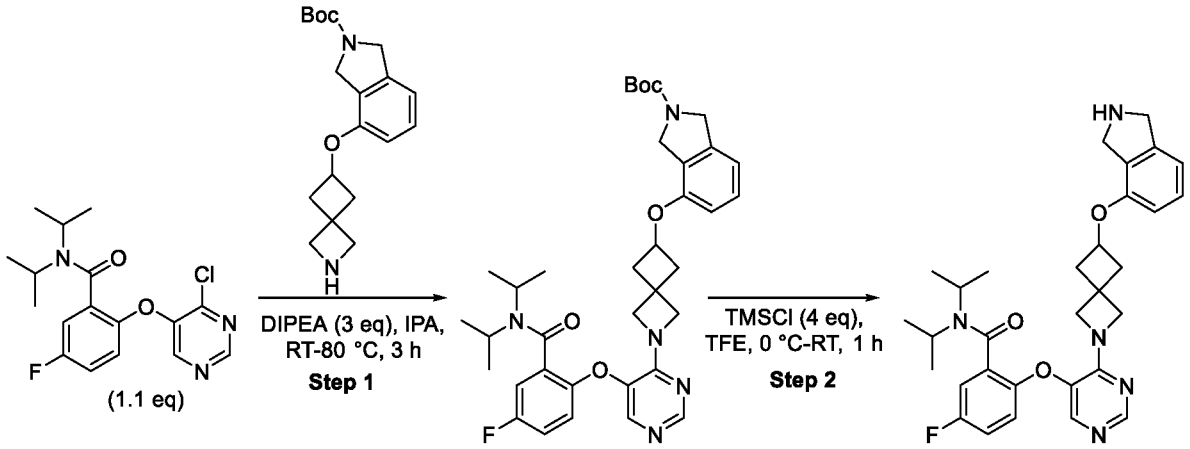
Step 5. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



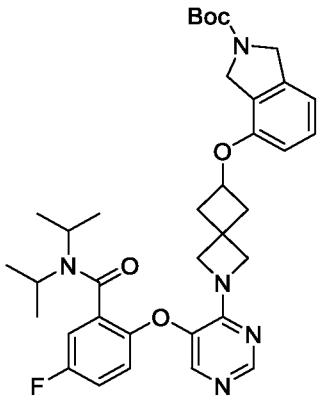
To a stirred solution of *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)methyl)-5,7-dihydro-6H-

pyrrolo[3,4-b]pyridine-6-carboxylate (30 mg, 0.048 mmol) in 2,2,2-trifluoroethanol (2 mL), TMSCl (0.024 mL, 0.190 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude was purified by Prep HPLC (Method J) to obtain 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (3.27 mg, 12.55% yield) as a solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.31 – 8.21 (m, 2H), 7.76 – 7.72 (m, 1H), 7.24 – 7.16 (m, 2H), 7.09 (d, *J* = 5.2 Hz, 1H), 7.01 – 6.93 (m, 1H), 4.36 – 4.07 (m, 8H), 3.91 (p, *J* = 6.7 Hz, 1H), 3.60 – 3.48 (m, 1H), 3.43 – 3.36 (m, 1H), 2.73 (d, *J* = 7.6 Hz, 2H), 2.61 – 2.49 (m, 1H), 2.41 – 2.26 (m, 2H), 2.07 – 1.91 (m, 2H), 1.36 – 1.15 (m, 9H). -NH proton was not observed. LCMS (Method H): Rt = 1.16 min, m/z = 531.2 $[M+H]^+$; HPLC (Method A): Rt = 4.43 min, 95.26%.

Example 40. 5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*,*N*-diisopropylbenzamide (Compound No. 3)



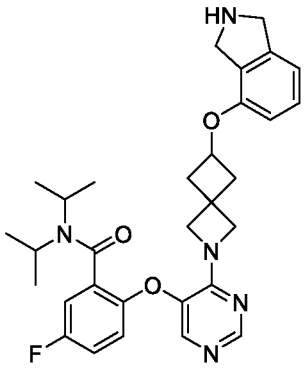
Step 1. tert-Butyl-4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1.1 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide and 1 equivalent of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate. After completion, the reaction was diluted with water and the mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate This material was used without further purification.

Yield: 96%; LCMS (Method H): Rt = 1.99 min, m/z = 646.9 $[M+H]^+$, 88.33%.

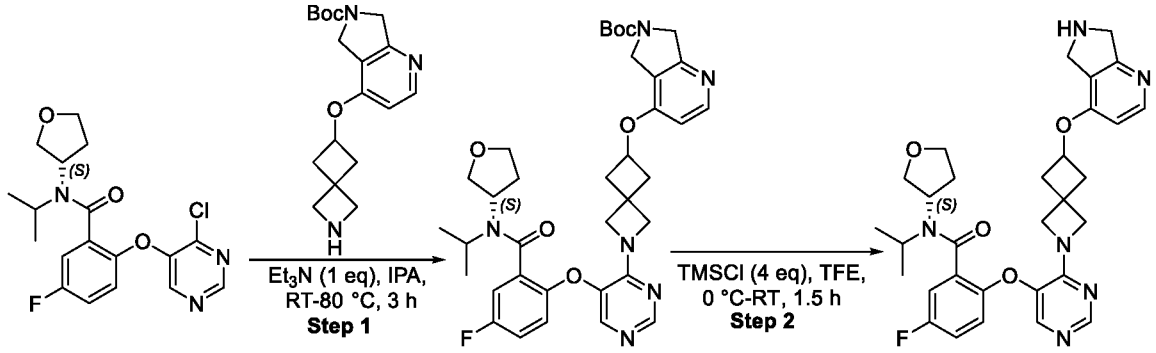
Step 2. 5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N,N-diisopropylbenzamide



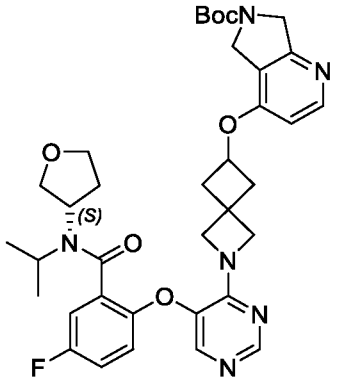
This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*,*N*-diisopropylbenzamide hydrochloride. The crude was purified by Prep HPLC (Method F) to afford 5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*,*N*-diisopropylbenzamide.

Yield: 30.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.73 (s, 1H), 7.28 - 7.19 (m, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.07 - 7.01 (m, 1H), 6.91 - 6.79 (m, 1H), 6.74 - 6.57 (m, 1H), 4.73 - 4.61 (m, 1H), 4.59 - 4.43 (m, 1H), 4.33 - 4.17 (m, 3H), 4.16 - 4.09 (m, 1H), 4.04 (s, 2H), 3.98 (s, 2H), 3.69 (spt, *J* = 6.6 Hz, 1H), 3.53 (spt, *J* = 6.8 Hz, 1H), 2.81 - 2.69 (m, 2H), 2.28 - 2.17 (m, 2H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); LCMS (Method D): Rt = 1.79 min, m/z = 546.3 $[M+H]^+$, 97.84% ; HPLC (Method A): Rt = 6.47 min, 98.37%.

Example 41. (*S*)-2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide (Compound No. 44)



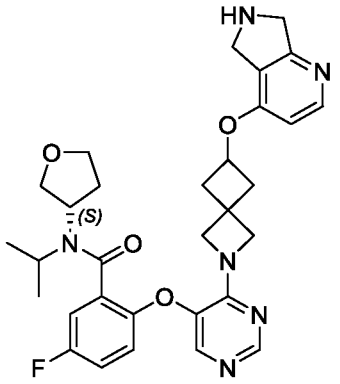
Step 1. tert-Butyl (S)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1 equivalent of (*S*)-2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide and 1 equivalent of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 1 equivalent of Et_3N was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (*S*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a solid.

Yield: 43.0%; LCMS (Method D): Rt = 1.98 min, m/z = 675.2 $[M+H]^+$, 79.57%.

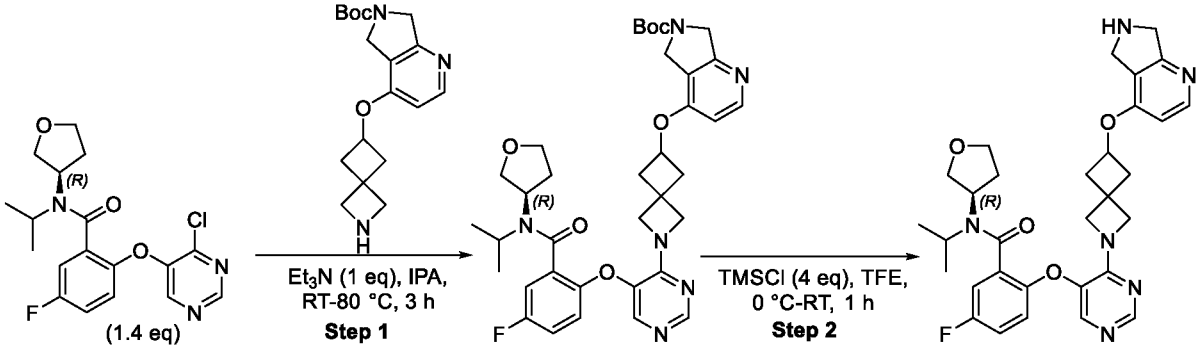
Step 2. (S)-2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydrofuran-3-yl)benzamide



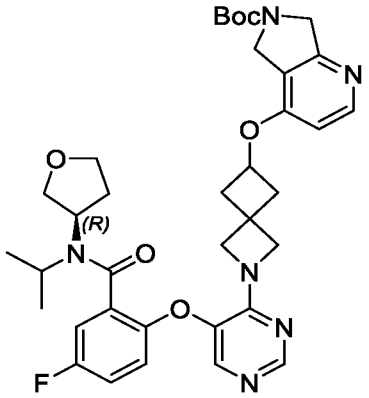
This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl (S)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate. After completion, the reaction was concentrated under reduced pressure to afford crude (*S*)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide hydrochloride. The crude was purified by Prep HPLC (Method B) to obtain (*S*)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide as a solid.

Yield: 31.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.21 (d, J = 5.7 Hz, 1H), 7.84 - 7.71 (m, 1H), 7.38 - 7.20 (m, 2H), 7.11 - 6.99 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.85 - 4.72 (m, 1H), 4.51 - 4.15 (m, 4H), 4.14 - 4.07 (m, 1H), 4.03 (br s, 2H), 3.99 (br s, 2H), 3.95 - 3.87 (m, 1H), 3.85 - 3.67 (m, 2H), 3.60 - 3.35 (m, 1H), 2.85 - 2.73 (m, 2H), 2.29 - 2.20 (m, 2H), 2.07 - 1.86 (m, 1H), 1.50 - 1.31 (m, 2H), 1.51 - 0.85 (m, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.55 min, m/z = 575.3 $[M+H]^+$; HPLC (Method A): Rt = 4.26min, 99.92%. Chiral SFC (Method J): Rt = 4.90 min, 97.73%.

Example 42. (*R*)-2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide (Compound No. 50)

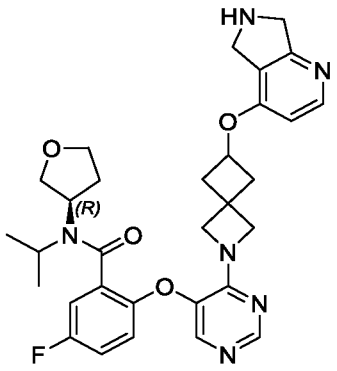


Step 1. tert-Butyl (R)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1.4 equivalents of (*R*)-2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide and 1 equivalent of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 1 equivalent of Et_3N was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *tert*-butyl (*R*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a semi-solid.
Yield: 43%; LCMS (Method D): Rt = 1.95 min, m/z = 675.6 $[M+H]^+$, 93.92%.

Step 2. (R)-2-((4-(6-(((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydrofuran-3-yl)benzamide

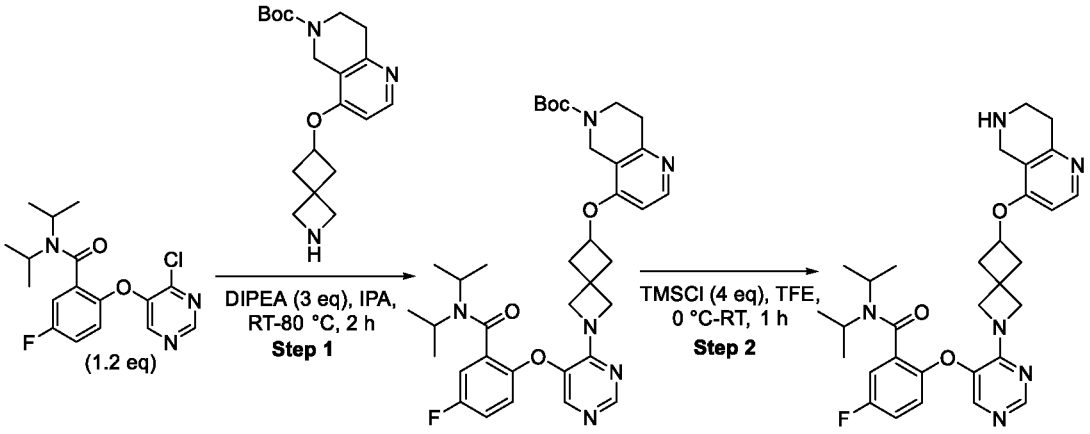


This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl (*R*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-

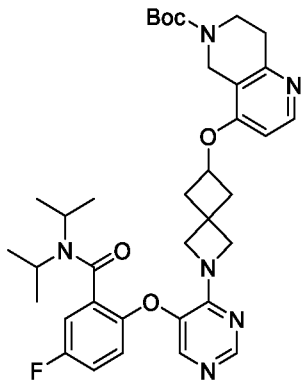
pyrrolo[3,4-b]pyridine-6-carboxylate. After completion, the reaction was concentrated under reduced pressure to afford crude (*R*)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide hydrochloride. The crude was purified by Prep HPLC (Method V) to obtain (*R*)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide as a solid.

Yield: 41.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.21 (d, *J* = 5.7 Hz, 1H), 7.85 - 7.71 (m, 1H), 7.36 - 7.20 (m, 2H), 7.10 - 6.98 (m, 1H), 6.68 (d, *J* = 5.8 Hz, 1H), 4.90 - 4.72 (m, 1H), 4.53 - 4.17 (m, 4H), 4.14 - 4.07 (m, 1H), 4.03 (br s, 2H), 3.99 (br s, 2H), 3.96 - 3.88 (m, 1H), 3.86 - 3.63 (m, 2H), 3.58 - 3.34 (m, 1H), 2.84 - 2.74 (m, 2H), 2.30 - 2.19 (m, 2H), 2.10 - 1.85 (m, 1H), 1.47- 1.31 (m, 2H), 1.14 - 0.93 (m, 6H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.52 min, m/z = 575.2 $[M+H]^+$; HPLC (Method A): Rt = 4.28 min, 97.08%; Chiral SFC (Method S): Rt = 2.50 min, 100%.

Example 43. 5-Fluoro-*N*,*N*-diisopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 52)



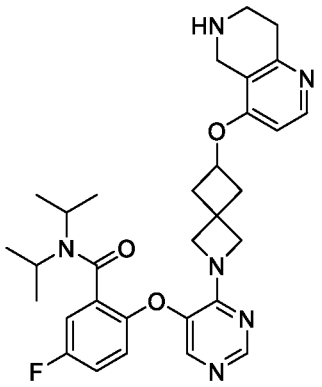
Step 1. tert-Butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1.2 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide was used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 3% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

Yield: 67.8%; LCMS (Method B): Rt = 2.02 min, m/z = 661.4 $[M+H]^+$, 97.94%.

Step 2. 5-Fluoro-N,N-diisopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

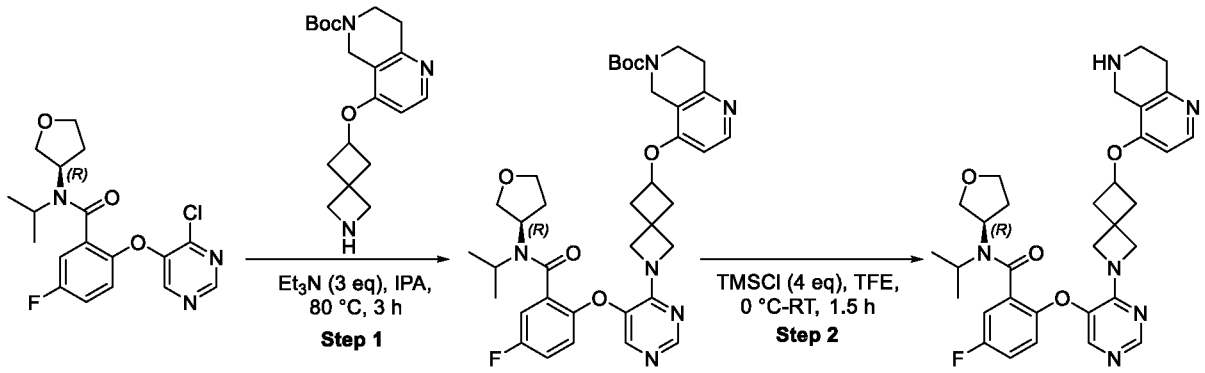


This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude 5-fluoro-*N*,*N*-diisopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 5-fluoro-*N*,*N*-diisopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

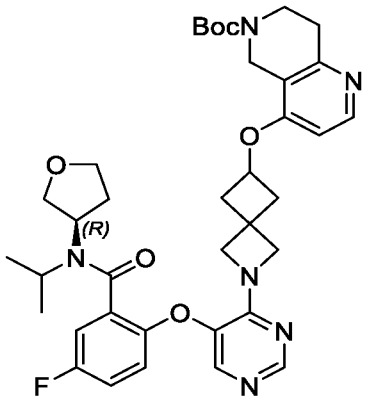
Yield: 35%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.16 (d, *J* = 5.7 Hz, 1H), 7.74 (s, 1H), 7.29 - 7.19 (m, 2H), 7.11 - 7.01 (m, 1H), 6.64 (d, *J* = 5.8 Hz, 1H), 4.73 (quin, *J* = 6.5 Hz, 1H), 4.34 - 4.09 (m, 4H), 3.74 - 3.63 (m, 3H), 3.59 - 3.46 (m, 1H), 2.95 (t, *J* = 5.8 Hz, 2H), 2.84 - 2.74 (m, 2H), 2.68 (br t, *J* = 5.5 Hz, 2H), 2.30 - 2.19 (m, 2H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H) one proton merged

with solvent peaks; LCMS (Method K): Rt = 1.44 min, m/z = 561.3 $[M+H]^+$; HPLC (Method A): Rt = 5.10 min, 99.05%.

Example 44. (*R*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydrofuran-3-yl)benzamide (Compound No. 54)



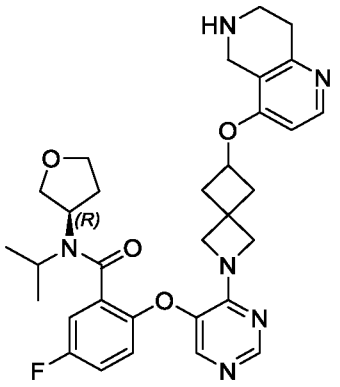
Step 1. tert-Butyl (R)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1 equivalent of (*R*)-2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide and 3 equivalents of Et_3N were used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *tert*-butyl (*R*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

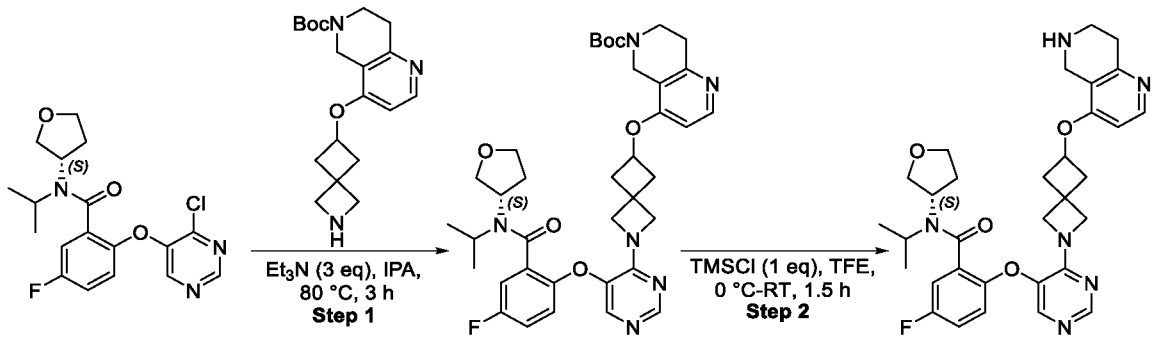
Yield: 34.0%; LCMS (Method C): Rt = 2.65 min, m/z = 689.4 $[M+H]^+$, 73.89%.

Step 2. (R)-5-Fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydrofuran-3-yl)benzamide

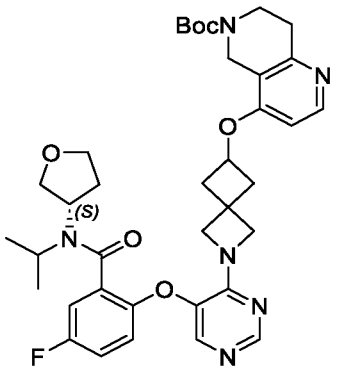


This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl (*R*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to afford crude (*R*)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydrofuran-3-yl)benzamide hydrochloride. The crude was purified by Prep HPLC (Method D) to obtain (*R*)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydrofuran-3-yl)benzamide as a solid. Yield: 41.6 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.16 (d, *J* = 5.6 Hz, 1H), 7.79 - 7.72 (m, 1H), 7.37 - 7.17 (m, 2H), 7.12 - 7.00 (m, 1H), 6.64 (d, *J* = 5.6 Hz, 1H), 4.74-4.71 (m, 1H), 4.39 - 4.07 (m, 5H), 4.06 - 3.87 (m, 2H), 3.84 - 3.65 (m, 4H), 3.51 - 3.35 (m, 2H), 2.95 (t, *J* = 5.8 Hz, 2H), 2.83 - 2.72 (m, 2H), 2.70 - 2.64 (m, 2H), 2.28 - 2.17 (m, 2H), 2.16 - 1.81 (m, 1H), 1.50 - 0.92 (m, 6H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.32 min, m/z = 589.4 $[M+H]^+$; HPLC (Method A): Rt = 4.59 min, 97.87%; Chiral SFC (Method V): Rt = 1.69 min, 97.46%.

Example 45. (*S*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydrofuran-3-yl)benzamide (Compound No. 57)



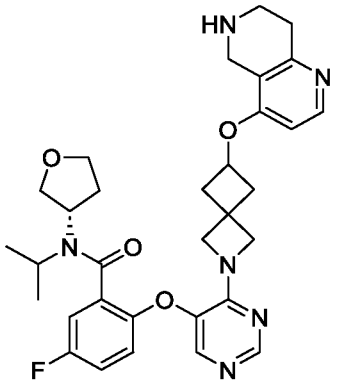
Step 1. tert-Butyl (S)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1 equivalent of (*S*)-2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydrofuran-3-yl)benzamide and 3 equivalents of Et_3N were used. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain *tert*-butyl (*S*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 58.0%; LCMS (Method D): Rt = 2.04 min, m/z = 689.4 $[M+H]^+$, 99.94%.

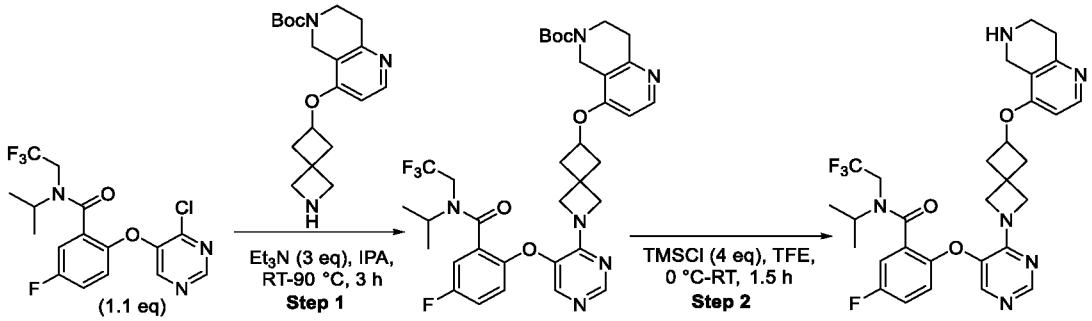
Step 2. (S)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydrofuran-3-yl)benzamide



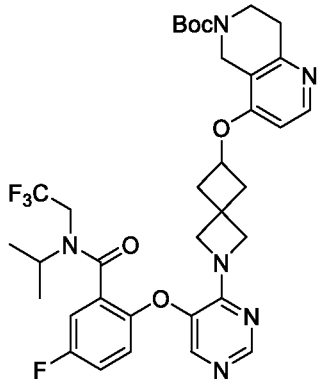
This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl (*S*)-4-((2-(5-(4-fluoro-2-(isopropyl(tetrahydrofuran-3-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1 equivalent of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to afford crude (*S*)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydrofuran-3-yl)benzamide hydrochloride. The crude was purified by achiral SFC (Method H) to obtain (*S*)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydrofuran-3-yl)benzamide as a solid.

Yield: 30.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 - 7.69 (m, 1H), 7.36 - 7.20 (m, 2H), 7.10 - 7.01 (m, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.75-4.70 (m, 1H), 4.36 - 4.07 (m, 5H), 4.05 - 3.88 (m, 2H), 3.86 - 3.64 (m, 4H), 3.60 - 3.34 (m, 2H), 2.98 (t, J = 5.9 Hz, 2H), 2.83 - 2.73 (m, 2H), 2.73 - 2.62 (m, 2H), 2.28 - 2.18 (m, 2H), 2.10 - 1.80 (m, 1H), 1.49 - 0.93 (m, 6H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.29 min, m/z = 589.2 $[M+H]^+$; HPLC (Method A): Rt = 4.52 min, 99.09%; Chiral SFC (Method W): Rt = 2.02 min, 93.79%.

Example 46. 5-Fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 67)



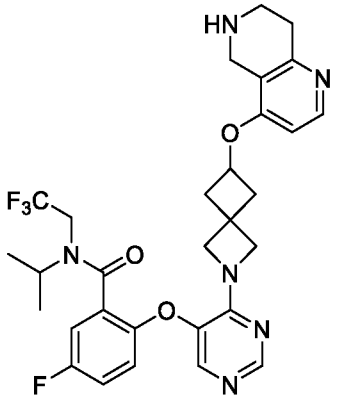
Step 1. tert-Butyl 4-((2-(5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1.1 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 3 equivalents of Et_3N were used. The reaction was stirred at 90 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *tert*-butyl 4-((2-(5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as semi-solid.

Yield: 69.0%; LCMS (Method C): Rt = 2.30 min, m/z = 701.2 $[M+H]^+$, 97.77%.

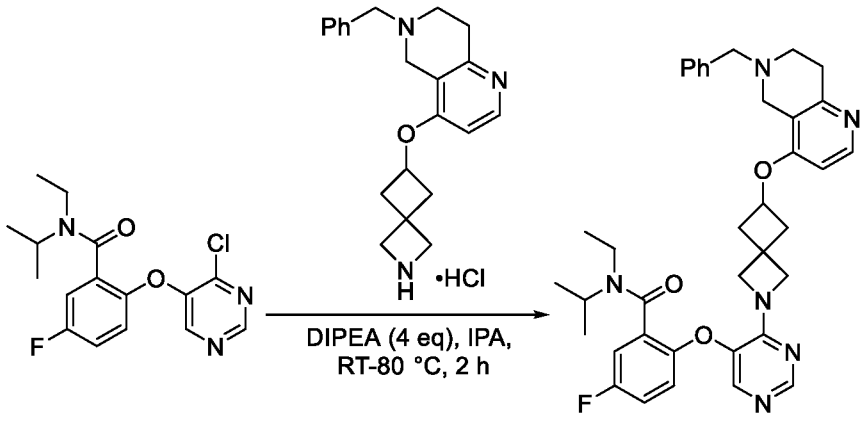
Step 2. 5-Fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



This compound was synthesized following the procedure described for the synthesis Example 1, step 2, starting with *tert*-butyl 4-((2-(5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was

concentrated under reduced pressure to obtain crude 5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride. The crude was purified by Prep HPLC (Method I) to obtain 5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide as a solid. Yield: 61.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.36 - 7.27 (m, 2H), 7.04-7.02 (m, 1H), 6.63 (d, J = 5.7 Hz, 1H), 4.77 - 4.66 (m, 1H), 4.43 - 4.02 (m, 6H), 3.99 - 3.87 (m, 1H), 3.69 (br s, 2H), 2.94 (t, J = 5.8 Hz, 2H), 2.84 - 2.72 (m, 2H), 2.67 (t, J = 5.8 Hz, 2H), 2.28 - 2.15 (m, 2H), 1.36 - 0.94 (m, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.79 min, m/z = 601.3 $[M+H]^+$; HPLC (Method A): Rt = 5.18 min, 98.93%.

Example 47. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 253)

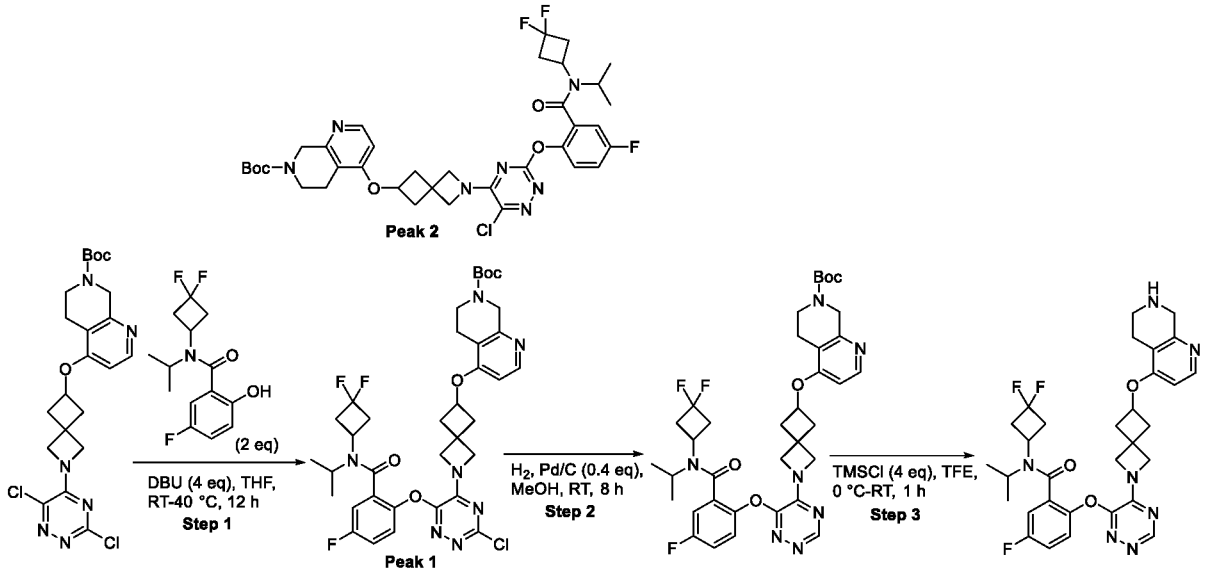


This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride and 4 equivalents of DIPEA were used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

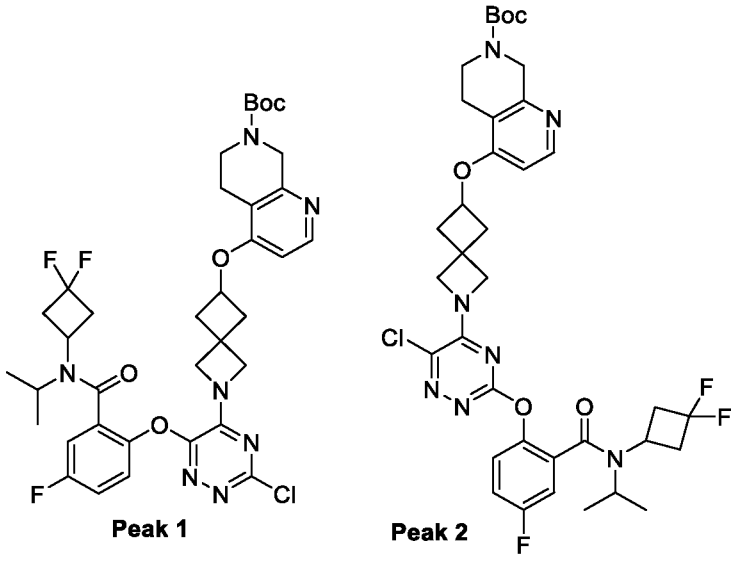
Yield: 30.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.17 (m, 1H), 7.76 - 7.66 (m, 1H), 7.37 - 7.33 (m, 4H), 7.33 - 7.22 (m, 3H), 7.10 - 7.00 (m, 1H), 6.69 - 6.65 (m, 1H), 4.77 - 4.67 (m, 1H), 4.46 - 4.04 (m, 4H), 3.79 - 3.71 (m, 1H), 3.68 (s, 2H), 3.47 (s, 2H),

3.43 - 3.37 (m, 1H), 3.27 - 3.20 (m, 1H), 2.83 - 2.70 (m, 6H), 2.26 - 2.16 (m, 2H), 1.15 - 0.97 (m, 9H); LCMS (Method G): Rt = 2.10 min, m/z = 637.6 $[M+H]^+$; HPLC (Method A): Rt = 6.22 min, 99.80%.

Example 48. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 201)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and 2 equivalents of *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide. The crude was purified by silica gel flash column chromatography using EtOAc (products were eluted at 100% EtOAc), then by achiral Prep SFC (Method E) to obtain both regioisomers.

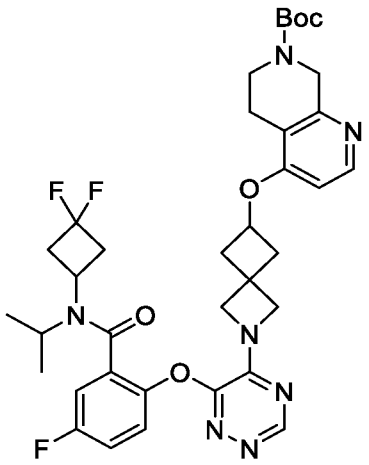
Peak 1. *tert*-Butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as a solid.

Yield: 23.87%; LCMS (Method G): Rt = 2.29 min, m/z = 744.6 $[M+H]^+$, 79.89%.

Peak 2. *tert*-Butyl 4-((2-(6-chloro-3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as white solid.

Yield: 15.91%; LCMS (Method G): Rt = 2.29 min, m/z = 744.6 $[M+H]^+$, 89.05%.

Step 2. tert-Butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate

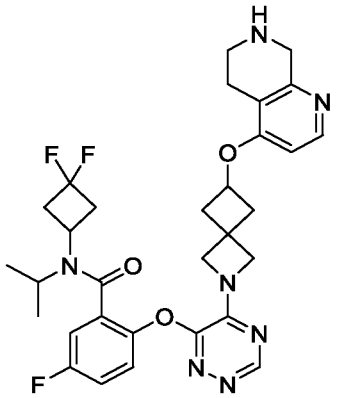


This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate, except that 0.4 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-

fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate. This material was used without further purification.

Yield: 88%; LCMS (Method G): Rt = 2.10 min, m/z = 710.6 $[M+H]^+$, 89.07%.

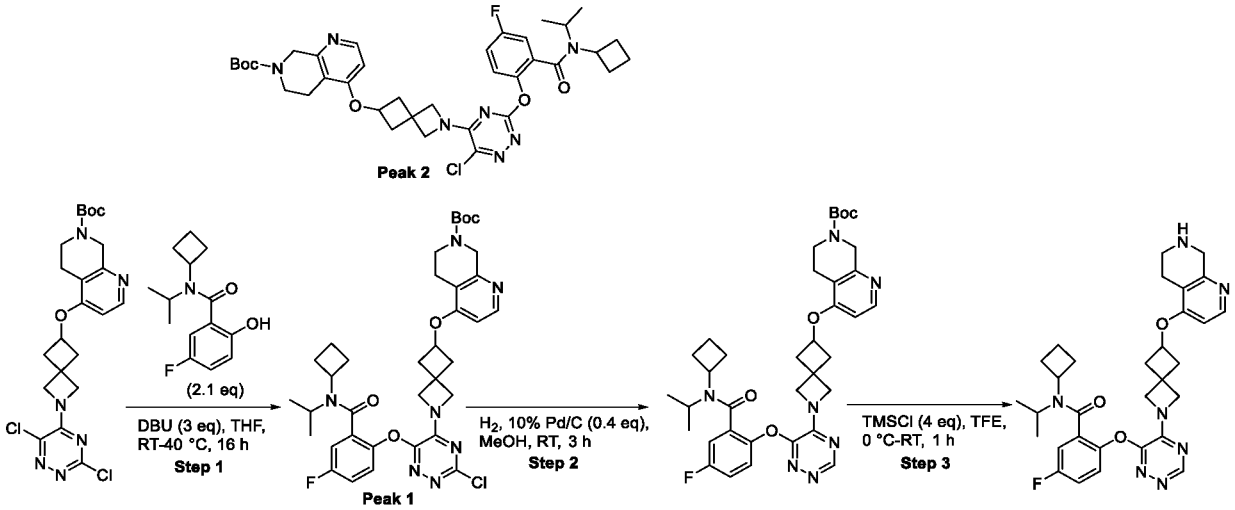
Step 3. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



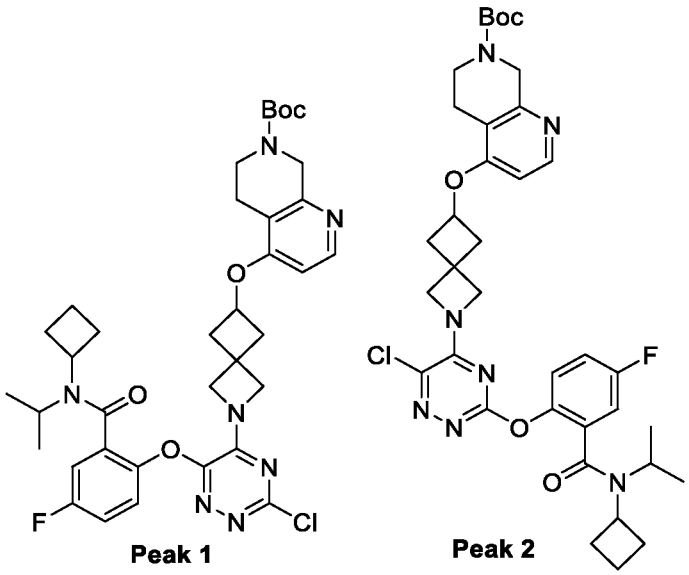
This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate. After completion, the reaction was concentrated under reduced pressure and the residue was triturated with EtOAc. The supernatant was decanted and the resulting residue was dried under reduced pressure to obtain crude *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 29.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.50 - 7.33 (m, 3H), 6.66 (br d, J = 3.8 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.68 - 4.50 (m, 2H), 4.30 - 4.14 (m, 2H), 3.85 (br s, 1H), 3.78 (s, 2H), 3.72 - 3.55 (m, 2H), 2.92 (br t, J = 5.3 Hz, 2H), 2.83 (br s, 3H), 2.74 - 2.62 (m, 2H), 2.35 - 2.30 (m, 2H), 1.44 - 0.57 (m, 6H), three protons merged with solvent peaks; LCMS (Method D): Rt = 1.76 min, m/z = 610.3 $[M+H]^+$; HPLC (Method A): Rt = 5.20 min, 97.93%.

Example 49. ***N*-Cyclobutyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide** (Compound No. 183)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate and tert-butyl 4-((2-(3-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate and 2.1 equivalents of *N*-cyclobutyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 3 equivalents of DBU was used. The crude product was purified by silica gel flash column

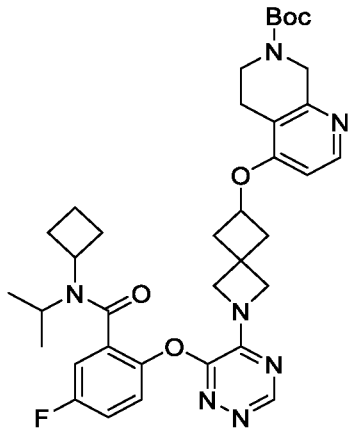
chromatography using EtOAc in hexane (products were eluted at 65% EtOAc in hexane) to obtain both regioisomers.

Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as a solid. Yield: 18.50%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 - 8.21 (m, 1H), 7.52 - 7.09 (m, 3H), 6.73 (d, J = 5.7 Hz, 1H), 4.85 - 4.55 (m, 3H), 4.45 (br s, 2H), 4.31 - 4.15 (m, 2H), 3.96 - 3.73 (m, 2H), 3.62 - 3.51 (m, 2H), 2.90 - 2.78 (m, 2H), 2.62 (br s, 2H), 2.39 - 2.27 (m, 2H), 2.12 - 1.89 (m, 2H), 1.72 - 1.50 (m, 1H), 1.45 - 1.39 (m, 12H), 1.28 - 0.67 (m, 6H); LCMS (Method B): Rt = 2.55 min, m/z = 708.3 $[M+H]^+$; 88.53%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as a sticky solid.

Yield: 2.11%; LCMS (Method B): Rt = 2.52 min, m/z = 708.2 $[M+H]^+$; 84.40%.

Step 2. tert-Butyl 4-((2-(6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate

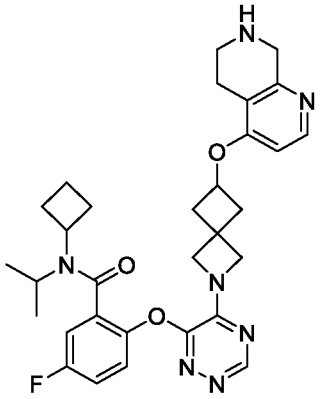


This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate, except that 0.4 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((2-(6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-

1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as a solid. This material was used without further purification.

Yield: 65.5%; LCMS (Method G): Rt = 2.28 min, m/z = 674.6 $[M+H]^+$; 81.03%.

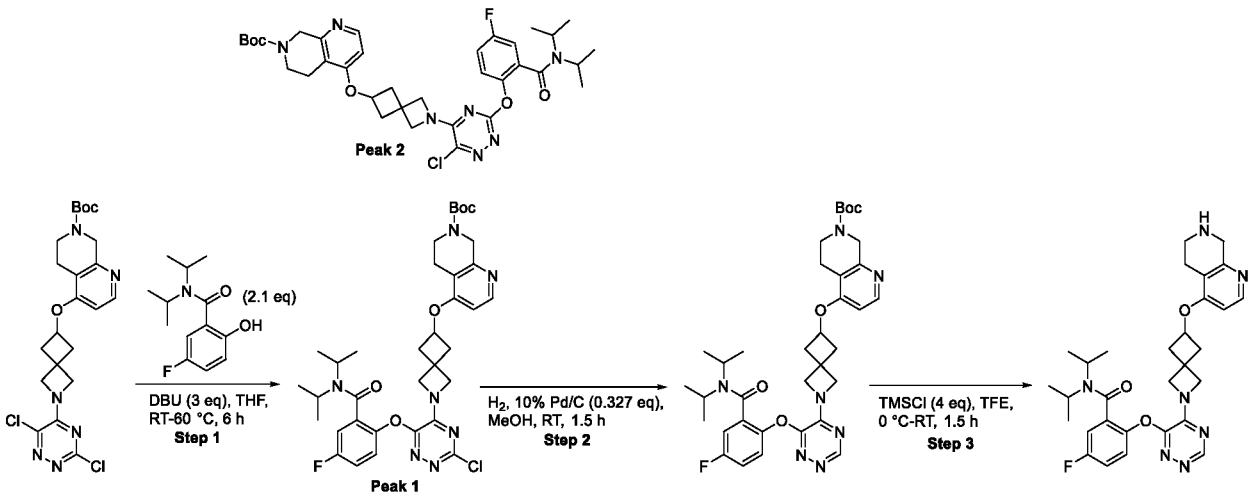
Step 3. N-Cyclobutyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



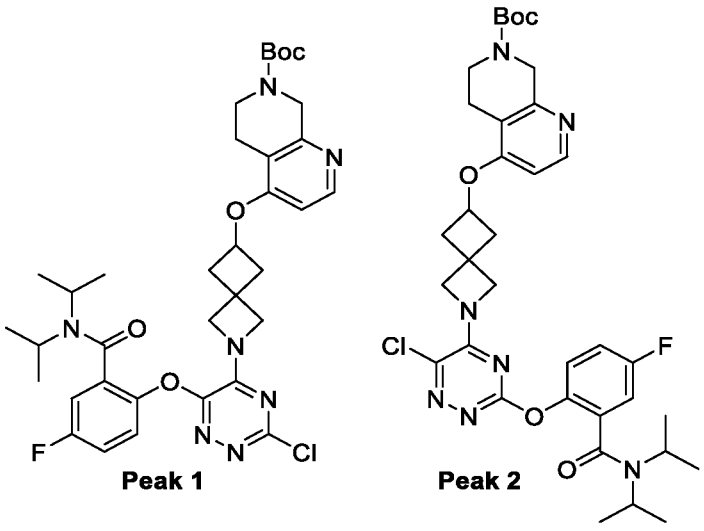
This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-cyclobutyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-cyclobutyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 45.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.15 (d, J = 5.7 Hz, 1H), 7.48 - 7.11 (m, 3H), 6.66 (d, J = 5.7 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.70 - 4.49 (m, 2H), 4.29 - 4.11 (m, 2H), 3.98 - 3.84 (m, 1H), 3.81 - 3.50 (m, 3H), 2.95 - 2.76 (m, 5H), 2.34 - 2.23 (m, 2H), 2.01 - 1.91 (m, 2H), 1.58 - 1.35 (m, 4H), 1.32 - 1.14 (m, 3H), 1.10 - 0.59 (m, 3H), two protons merged with solvent peak; LCMS (Method D): Rt = 1.75 min, m/z = 574.4 $[M+H]^+$; HPLC (Method D): Rt = 2.94 min, 96.62%.

Example 50. 5-Fluoro-*N*, *N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 151)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



This compound was synthesized by following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate and 2.1 equivalents of 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide, except that 3 equivalents of DBU was used. The reaction was stirred at 60 °C. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 65% EtOAc in hexane) to obtain both regioisomers.

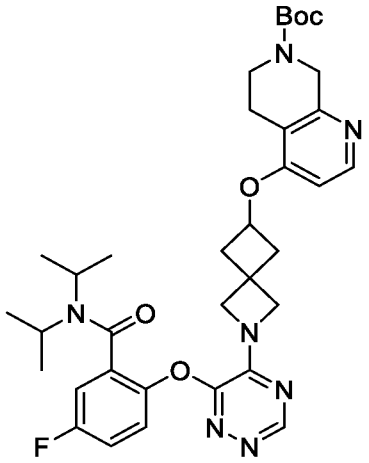
Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as a solid.

Yield: 28.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 - 8.22 (m, 1H), 7.48 - 7.40 (m, 1H), 7.39 - 7.26 (m, 2H), 6.73 (dd, J = 3.0, 5.5 Hz, 1H), 4.85 - 4.75 (m, 1H), 4.72 - 4.59 (m, 2H), 4.45 (br s, 2H), 4.30 - 4.17 (m, 2H), 3.63 - 3.43 (m, 4H), 2.88 - 2.73 (m, 2H), 2.62 (br t, J = 5.8 Hz, 2H), 2.39 - 2.26 (m, 1H), 1.46 - 1.37 (m, 12H), 1.34 - 1.26 (m, 3H), 1.13 - 1.03 (m, 3H), 0.72 (br d, J = 6.3 Hz, 3H), one proton merged with solvent peak; LCMS (Method B): Rt = 2.34 min, m/z = 696.2 $[M+H]^+$; 95.05%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate as a solid.

Yield: 7.75%; LCMS (Method B): Rt = 2.47 min, m/z = 696.2 $[M+H]^+$; 85.91%.

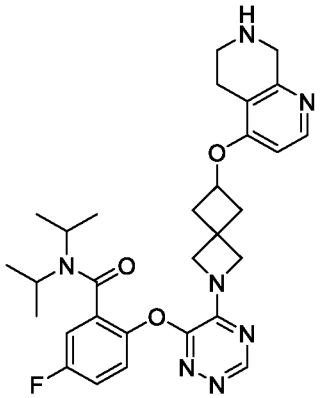
Step 2. tert-Butyl 4-((2-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate, except that 0.327 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to obtain *tert*-butyl 4-((2-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate.

Yield: 61.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.24 (d, J = 5.5 Hz, 1H), 7.47 - 7.41 (m, 1H), 7.38 - 7.25 (m, 2H), 6.74 (d, J = 5.6 Hz, 1H), 4.87 - 4.75 (m, 1H), 4.71 - 4.53 (m, 2H), 4.46 (s, 2H), 4.31 - 4.12 (m, 2H), 3.62 - 3.39 (m, 5H), 2.83 (br s, 2H), 2.63 (t, J = 5.6 Hz, 2H), 2.38 - 2.27 (m, 1H), 1.49 - 1.36 (m, 12H), 1.28 (d, J = 4.9 Hz, 3H), 1.07 (d, J = 6.0 Hz, 3H), 0.64 (d, J = 6.4 Hz, 3H); LCMS (Method G): Rt = 2.07 min, m/z = 662.6 $[M+H]^+$; 89.54%.

Step 3. 5-Fluoro-N,N-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

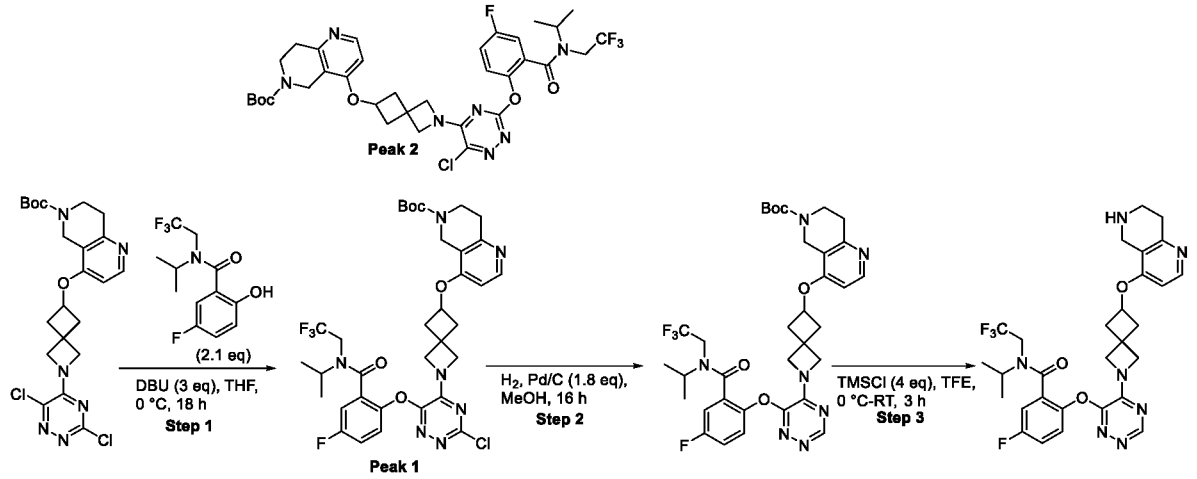


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the product. The isolated product showed impurity peaks in ^{1}HNMR. Therefore, water was added to the compound. The mixture was basified with saturated sodium bicarbonate and extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and lyophilized to obtain 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

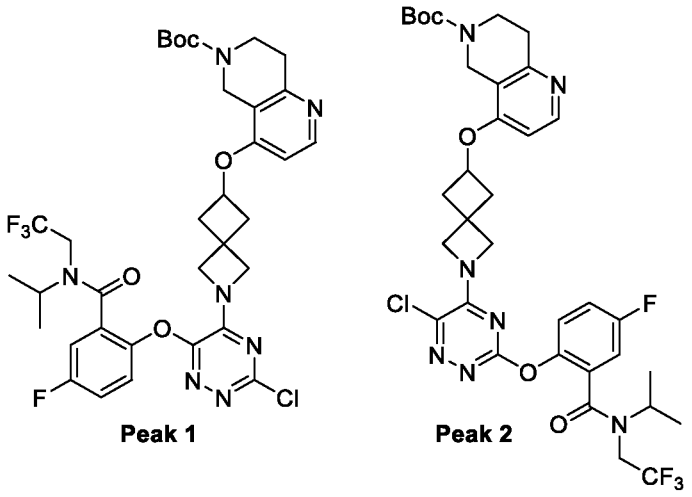
Yield: 21.97%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.38 - 7.26 (m, 2H), 6.71 (d, J = 5.8 Hz, 1H), 4.84 - 4.76 (m, 1H), 4.70 - 4.53 (m, 2H), 4.31 - 4.08 (m, 2H), 3.88 (s, 2H), 3.61 - 3.40 (m, 2H), 3.03 (br t, J = 5.6 Hz, 2H), 2.89

- 2.74 (m, 2H), 2.63 - 2.56 (m, 3H), 2.37 - 2.26 (m, 1H), 1.42 (br s, 3H), 1.28 (br s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.63 (d, *J* = 6.5 Hz, 3H), one proton merged with solvent peak; LCMS (Method B): Rt = 1.61 min, m/z = 562.4 $[M+H]^+$; HPLC (Method D): Rt = 2.66 min, 97.96%.

Example 51. 5-Fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 235)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and tert-butyl 4-((2-(6-chloro-3-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 2.1 equivalents of 5-fluoro-2-hydroxy-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 3

equivalents of DBU were used. The reaction was stirred at RT. After work-up, the crude product was purified by silica gel flash column chromatography using EtOAc (products were eluted at 100% EtOAc) to obtain a mixture of *tert*-butyl 4-((2-(3-chloro-6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and the other regioisomer as a solid. The mixture was re-purified by chiral Prep SFC (Method C) to obtain both regioisomers.

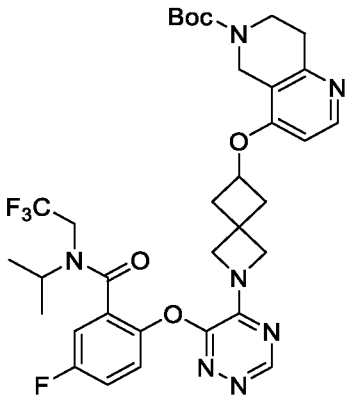
Peak 1. *tert*-Butyl 4-((2-(3-chloro-6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 33.5%; LCMS (Method G): Rt = 2.27 min, m/z = 736.6 $[M+H]^+$, 100%.

Peak 2. *tert*-Butyl 4-((2-(6-chloro-3-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 21.02%; LCMS (Method G): Rt = 2.30 min, m/z = 736.6 $[M+H]^+$, 98.20%.

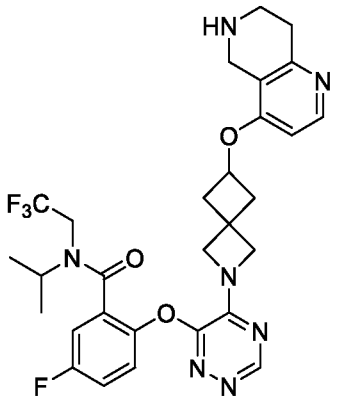
Step 2. tert-Butyl 4-((2-(6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1.8 equivalents of Pd/C was used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to obtain *tert*-butyl 4-((2-(6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

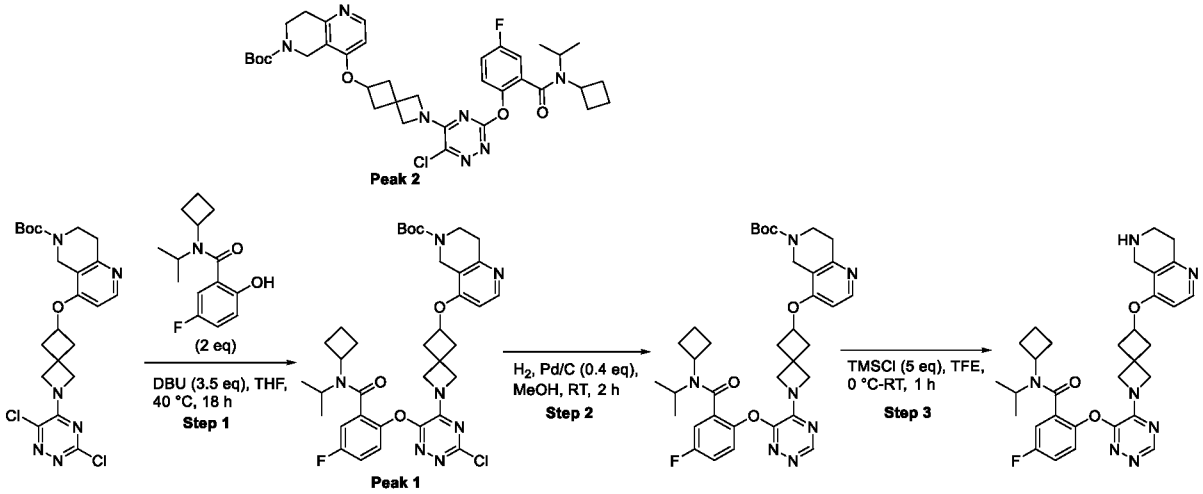
Yield: 75%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.25 (d, J = 5.5 Hz, 1H), 7.53 - 7.36 (m, 3H), 6.76 (d, J = 5.0 Hz, 1H), 4.82 (quin, J = 6.4 Hz, 1H), 4.65 - 4.44 (m, 2H), 4.38 (s, 2H), 4.31 - 4.02 (m, 4H), 3.83 - 3.73 (m, 1H), 3.68 - 3.56 (m, 2H), 2.92 - 2.76 (m, 4H), 2.41 - 2.25 (m, 2H), 1.43 (s, 9H), 1.27 - 0.67 (m, 6H); LCMS (Method D): Rt = 2.14 min, m/z = 702.4 $[M+H]^+$, 99.75%.

Step 3. 5-Fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide

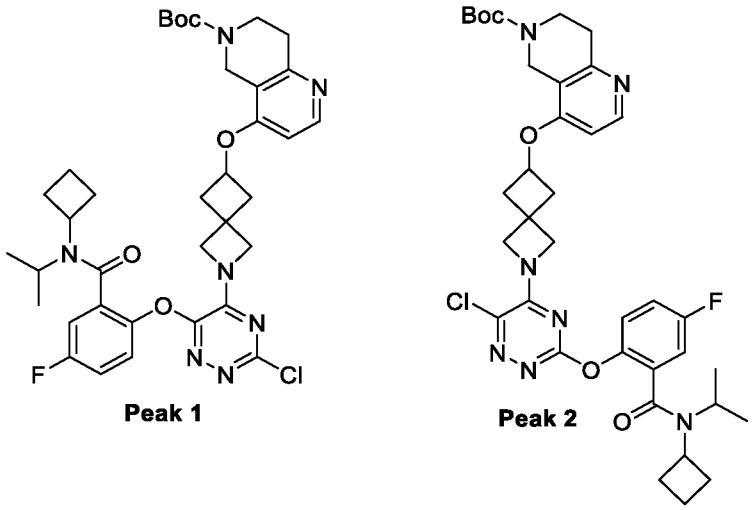


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc. The organic layer was decanted, and the solid was dried under vacuum to obtain crude 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide as a solid. Yield: 63.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.55 - 7.39 (m, 3H), 6.66 (br d, J = 4.1 Hz, 1H), 4.77 (quin, J = 6.6 Hz, 1H), 4.65 - 4.42 (m, 2H), 4.34 - 4.00 (m, 4H), 3.84 - 3.75 (m, 1H), 3.70 (s, 2H), 2.95 (br t, J = 5.6 Hz, 2H), 2.87 - 2.82 (m, 2H), 2.72 - 2.65 (m, 3H), 2.33 - 2.23 (m, 1H), 1.26 - 0.68 (m, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.68 min, m/z = 602.3 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 99.74%.

Example 52. ***N*-Cyclobutyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide** (Compound No. 179)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

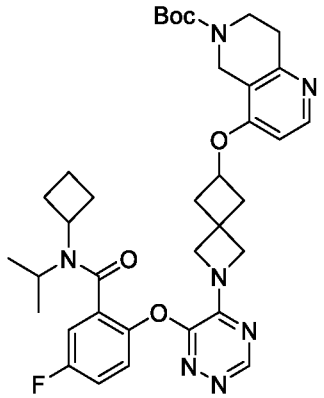


This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 2 equivalents of *N*-cyclobutyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide and 3.5 equivalents of DBU were used. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted in 70% EtOAc in hexane) to obtain pure peak 1.

Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. Yield: 26.7%; LCMS (Method D): Rt = 2.44 min, m/z = 708.4 $[M+H]^+$, 88.41%.

Note: Peak 2 was not isolated.

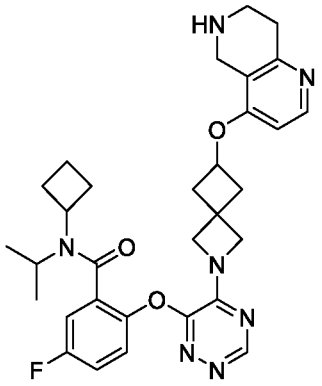
Step 2. tert-Butyl 4-((2-(6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 0.4 equivalent of Pd-C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 4-((2-(6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a gummy solid. This material was used without further purification.

Yield: 80%; LCMS (Method G): Rt = 2.14 min, m/z = 674.7 $[M+H]^+$; 87.98%.

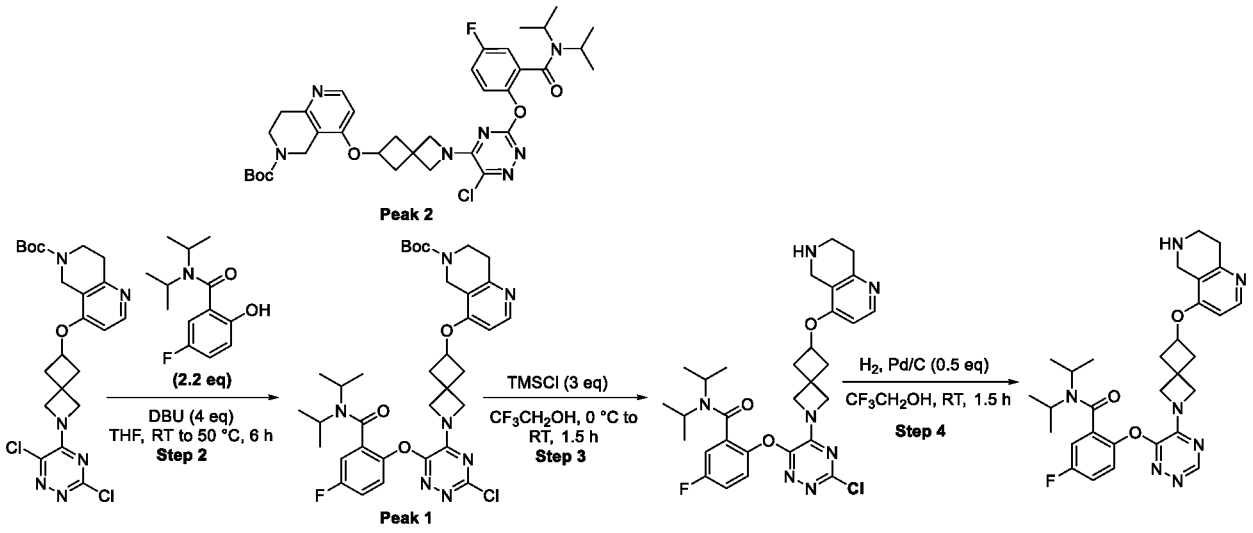
Step 3. N-Cyclobutyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



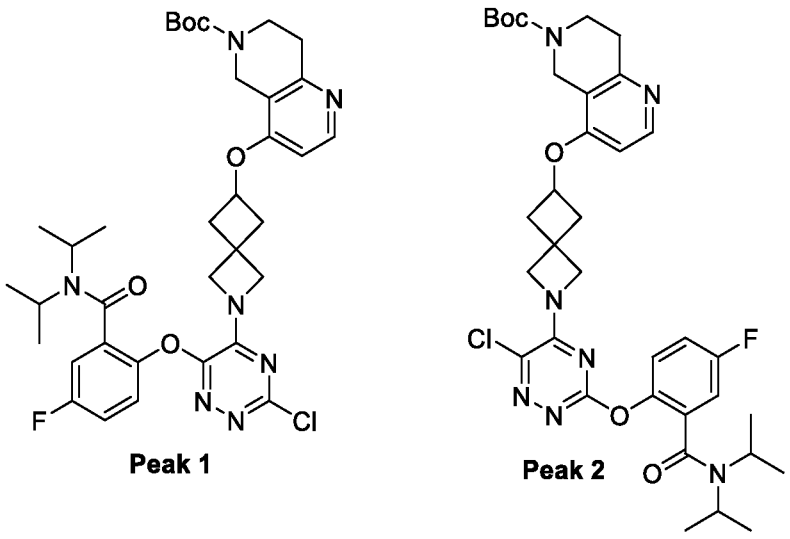
This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-(cyclobutyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 5 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to afford crude *N*-cyclobutyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-cyclobutyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 28.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (br s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.40 - 7.27 (m, 1H), 7.20 - 7.11 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.77 (quin, J = 6.5 Hz, 1H), 4.71 - 4.45 (m, 2H), 4.31 - 4.08 (m, 2H), 3.97 - 3.81 (m, 1H), 3.81 - 3.73 (m, 1H), 3.70 (s, 2H), 3.61 - 3.44 (m, 1H), 3.15 - 3.00 (m, 1H), 2.95 (br t, J = 5.6 Hz, 2H), 2.87 - 2.74 (m, 2H), 2.71 - 2.64 (m, 2H), 2.32 - 2.22 (m, 2H), 2.14 - 1.87 (m, 3H), 1.79 - 0.55 (m, 8H); LCMS (Method G): Rt = 1.72 min, m/z = 574.6 $[M+H]^+$; HPLC (Method E): Rt = 3.30 min, 98.50%.

Example 53. 5-Fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 105)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 2.2 equivalents of 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide was used. The reaction was stirred at 50 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 80% EtOAc in hexane) to obtain both regioisomers.

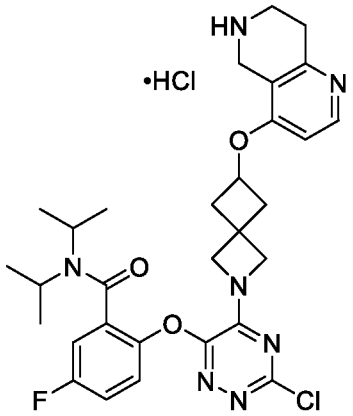
Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

Yield: 33%; LCMS (Method B): Rt = 2.41 min, m/z = 696.2 $[M+H]^+$, 72.85%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

Yield: 11.12%; LCMS (Method G): Rt = 2.38 min, m/z = 696.2 $[M+H]^+$, 31.39%.

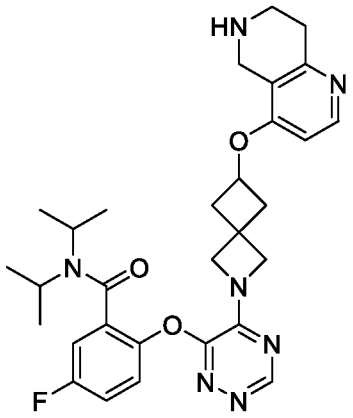
Step 2. 2-((3-Chloro-5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 3 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure. The residue was triturated with EtOAc, and the solid was dried under reduced pressure to obtain crude 2-((3-chloro-5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N,N*-diisopropylbenzamide hydrochloride as a solid.

Yield: 64.1%; LCMS (Method G): Rt = 1.74 min, m/z = 596.3 $[M+H]^+$, 96.17%.

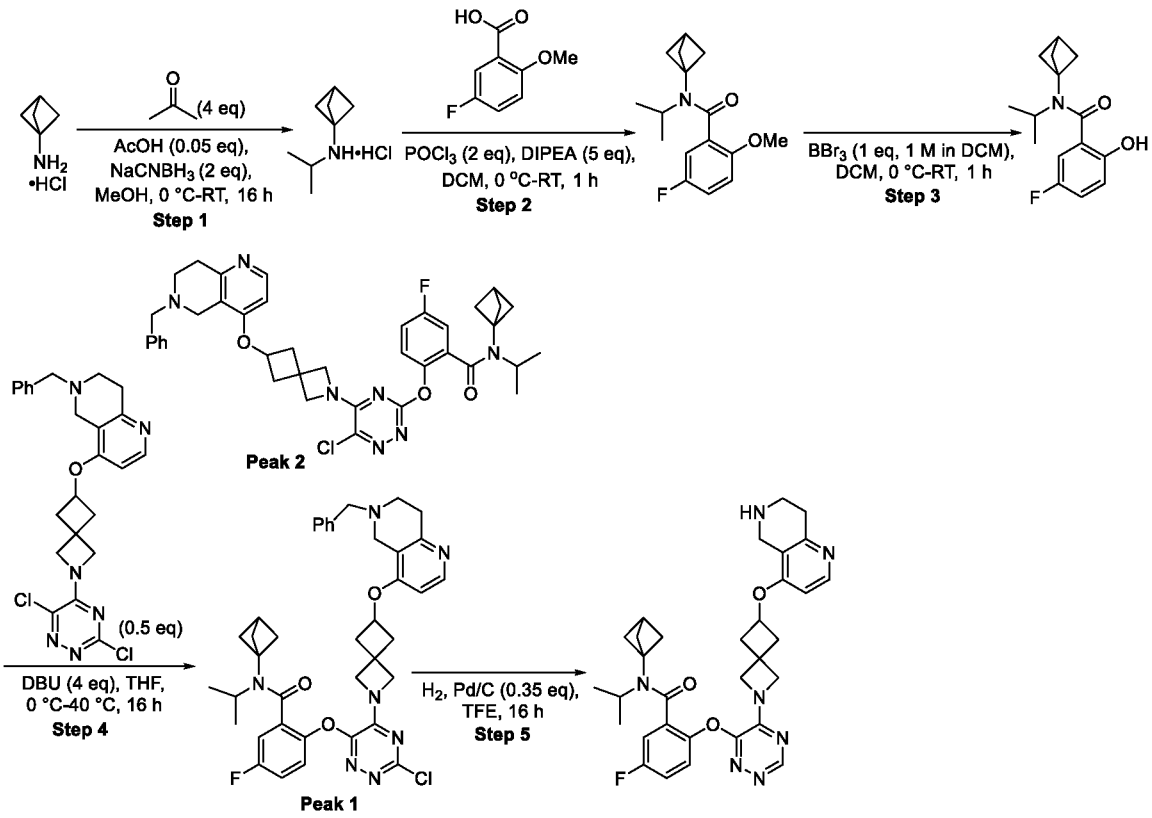
Step 3. 5-Fluoro-N,N-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



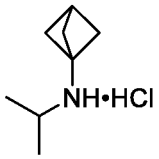
This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with 2-((3-chloro-5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide hydrochloride, except that 0.5 equivalent of Pd-C was used, and TFE was used as a solvent. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure to obtain crude 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 57.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.44 (dd, J = 4.6, 8.9 Hz, 1H), 7.39 - 7.23 (m, 2H), 6.66 (d, J = 5.8 Hz, 1H), 4.77 (quin, J = 6.4 Hz, 1H), 4.71 - 4.49 (m, 2H), 4.37 - 4.02 (m, 2H), 3.71 (s, 2H), 3.63 - 3.52 (m, 1H), 3.45 (spt, J = 6.6 Hz, 1H), 2.95 (br t, J = 5.7 Hz, 2H), 2.88 - 2.75 (m, 2H), 2.68 (br t, J = 5.0 Hz, 2H), 2.44 - 2.06 (m, 3H), 1.42 (br s, 3H), 1.28 (br s, 3H), 1.07 (br d, J = 6.3 Hz, 3H), 0.64 (br d, J = 6.4 Hz, 3H); LCMS (Method G): Rt = 1.63 min, m/z = 562.5 $[M+H]^+$; HPLC (Method A): Rt = 4.79 min, 98.26%.

Example 54. *N*-(Bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 310)

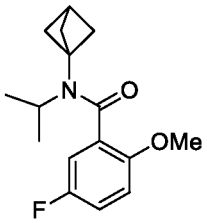


Step 1. N-Isopropylbicyclo[1.1.1]pentan-1-amine hydrochloride



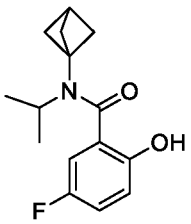
In a 250 mL round bottom flask under a nitrogen atmosphere, bicyclo[1.1.1]pentan-1-amine hydrochloride (2.5 g, 20.90 mmol) was added in MeOH (350 mL) at RT. To this solution, acetone (6.14 mL, 84 mmol) and AcOH (0.060 mL, 1.045 mmol) were added, and the reaction was stirred at RT for 2 h. The reaction was cooled to 0 °C, and sodium cyanoborohydride (2.63 g, 41.8 mmol) was added. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 30 mL). The filtrate was cooled to 0 °C, 4M HCl in 1,4-dioxane (5 mL) was added, and the mixture was stirred at RT for 30 min. The solvent was evaporated under reduced pressure to obtain crude *N*-isopropylbicyclo[1.1.1]pentan-1-amine hydrochloride (3.0 g, 89% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (br s, 2 H), 3.16 - 3.10 (m, 1H), 1.95 (br s, 6H), 1.13 (d, J = 6.4 Hz, 6H). This material was used without further purification.

Step 2. N-(Bicyclo[1.1.1]pentan-1-yl)-5-fluoro-N-isopropyl-2-methoxybenzamide



In a 250 mL round bottom flask under a nitrogen atmosphere, 5-fluoro-2-methoxybenzoic acid (3 g, 17.63 mmol) and *N*-isopropylbicyclo[1.1.1]pentan-1-amine hydrochloride (2.85 g, 17.63 mmol) were added in DCM (40 mL). DIPEA (15.40 mL, 88 mmol) and $POCl_3$ (3.29 mL, 35.3 mmol) were added to this reaction mixture at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with cold water (100 mL), and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain *N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide (3.123 g, 58.0% yield) as a semi-solid. LCMS (Method G): Rt = 2.11 min, m/z = 278.3 $[M+H]^+$, 90.85%.

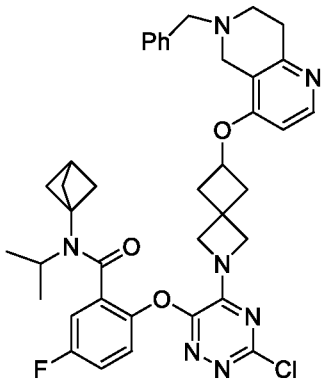
Step 3. N-(Bicyclo[1.1.1]pentan-1-yl)-5-fluoro-2-hydroxy-N-isopropylbenzamide



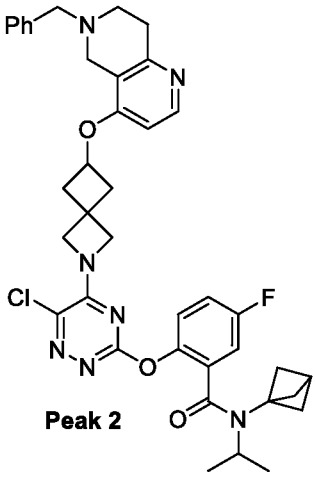
To a stirred solution of *N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide (3.0 g, 10.82 mmol) in DCM (30 mL), BBr_3 (10.82 mL, 10.82 mmol, 1M in DCM) was added slowly at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with ice-cold water (100 mL), and extracted with DCM (3 x 50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain *N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (2.75 g, 92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (br s, 1H), 7.05 - 6.98 (m, 1H), 6.87 - 6.83

(m, 1H), 6.83 - 6.78 (m, 1H), 4.02 - 3.86 (m, 1H), 2.30 - 2.25 (m, 1H), 1.94 (br s, 6H), 1.29 (d, *J* = 6.9 Hz, 6H); LCMS (Method G): Rt = 1.91 min, m/z = 264.2 $[M+H]^+$, 95.61%.

Step 4. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-N-isopropylbenzamide



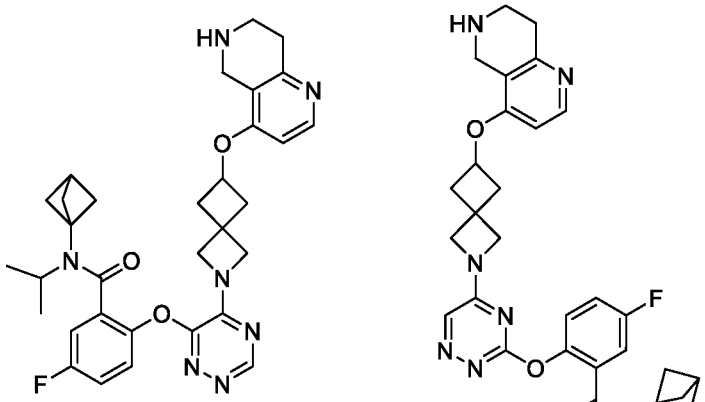
Peak 1



Peak 2

To a stirred solution of *N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (1.00 g, 3.80 mmol) in THF (15 mL), DBU (2.290 mL, 15.19 mmol) was added at 0 °C. To this reaction mixture, 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine (0.918 g, 1.899 mmol) was added. The reaction was stirred at 40 °C for 16 h. The progress of the reaction was monitored by LCMS (Method D). After completion, the reaction was quenched with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropylbenzamide (1.00 g, 30.7% yield) as a solid. LCMS (Method G): Rt = 2.47 min, m/z = 710.6 $[M+H]^+$, 82.84%. The mixture of regioisomers were used without further purification.

Step 5. N-(Bicyclo[1.1.1]pentan-1-yl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and N-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide

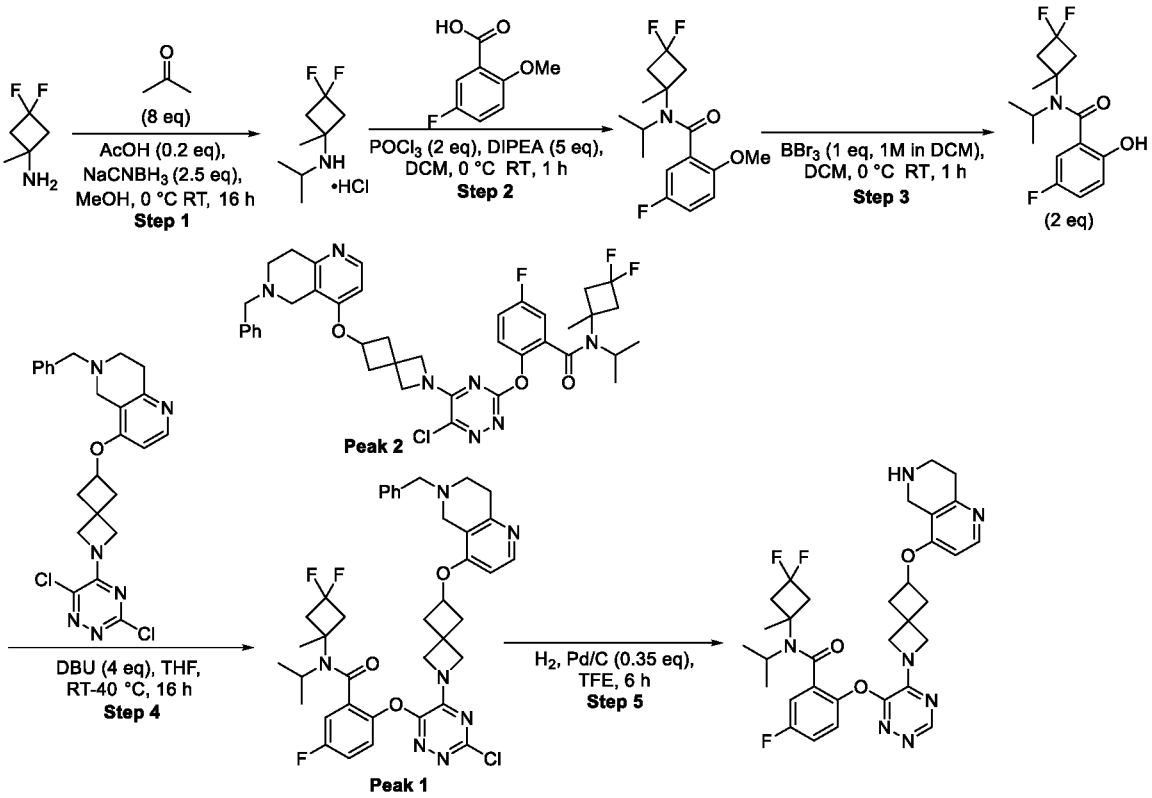


In a 100 mL round bottom flask under an argon atmosphere, a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-(bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropylbenzamide (0.500 g, 0.704 mmol) was added in 2,2,2-trifloroethanol (10 mL). Pd-C (0.262 g, 0.246 mmol) was added to this solution, and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude was purified by Prep HPLC purification (method AD) to obtain both isomers.

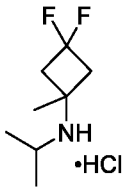
Peak 1. *N*-(Bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (128.01 mg, 31.0% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 - 8.45 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.39 - 7.23 (m, 2H), 6.66 (d, J = 5.5 Hz, 1H), 4.82 - 4.73 (m, 1H), 4.69 - 4.42 (m, 2H), 4.28 - 4.12 (m, 2H), 4.06 - 3.86 (m, 1H), 3.70 (br s, 2H), 2.98 - 2.92 (m, 2H), 2.90 - 2.76 (m, 2H), 2.72 - 2.65 (m, 2H), 2.37 - 2.18 (m, 6H), 1.80 (br s, 2H), 1.63 (br s, 2H), 1.40 - 1.14 (m, 6H); LCMS (Method G): Rt = 1.73 min, m/z = 586.5 $[M+H]^+$; HPLC (Method A): Rt = 4.87 min, 99.77%.

Peak 2. *N*-(Bicyclo[1.1.1]pentan-1-yl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide (80 mg, 19.08% yield) as a solid. LCMS (Method G): Rt = 2.21 min, m/z = 586.3 $[M+H]^+$, 98.33%.

Example 55. *N*-(3,3-Difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 261)



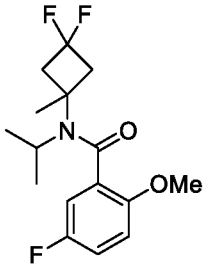
Step 1. 3,3-Difluoro-N-isopropyl-1-methylcyclobutan-1-amine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 54, step 1, starting with 8 equivalents of acetone, except that 3,3-difluoro-1-methylcyclobutan-1-amine, 0.2 equivalent of acetic acid, and 2.5 equivalents of sodium cyanoborohydride were used to obtain crude 3,3-difluoro-*N*-isopropyl-1-methylcyclobutan-1-amine hydrochloride.

Yield: 95%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.83 (br s, 2H), 3.50 - 3.37 (m, 1H), 3.29 - 3.18 (m, 2H), 2.78 - 2.67 (m, 2H), 1.48 (s, 3H), 1.24 (d, J = 6.5 Hz, 6H). This material was used without further purification.

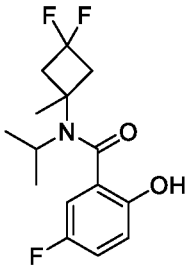
Step 2. *N*-(3,3-Difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide



This compound was synthesized following the procedure described for the synthesis of Example 54, step 2, starting with 5-fluoro-2-methoxybenzoic acid, except that 1 equivalent of 3,3-difluoro-*N*-isopropyl-1-methylcyclobutan-1-amine hydrochloride was used. The crude was purified by silica gel flash column chromatography using 20% EtOAc in hexane to obtain *N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide.

Yield: 25.3%; LCMS (Method G): Rt = 2.06 min, m/z = 316.3 $[M+H]^+$, 91.89%.

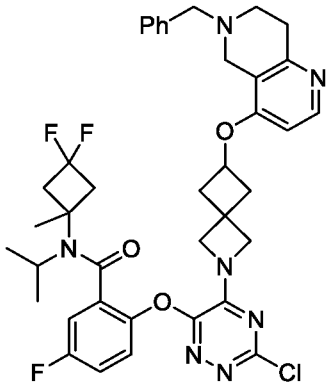
Step 3. *N*-(3,3-Difluoro-1-methylcyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide



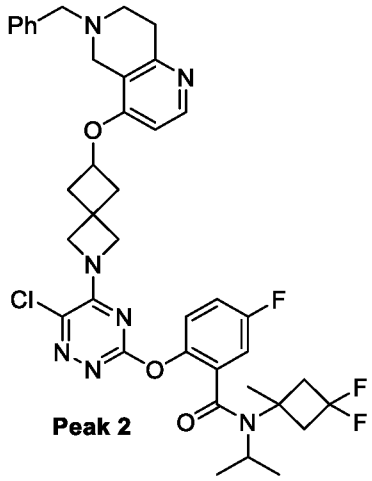
This compound was synthesized following the procedure described for the synthesis of Example 54, step 3, starting with *N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-methoxybenzamide. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 15-20% EtOAc in hexane) to obtain *N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide.

Yield: 76%; LCMS (Method G): Rt = 1.85 min, m/z = 302.2 $[M+H]^+$, 95.47%.

Step 4. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-N-isopropylbenzamide



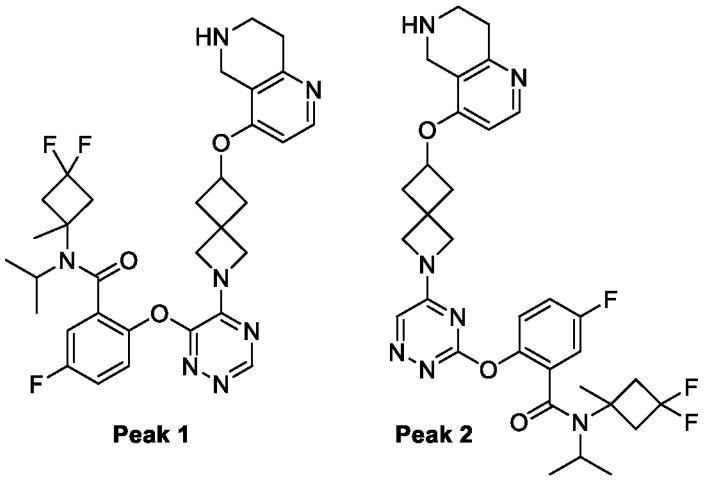
Peak 1



Peak 2

This compound was synthesized following the procedure described for the synthesis of Example 54, step 4, starting with 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine, except that 2 equivalents of *N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide was used. The crude was purified by silica gel flash column chromatography using 10% MeOH in DCM to obtain a mixture of both regioisomers, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropylbenzamide. Yield: 41.8%; LCMS (Method G): Rt = 2.38 min, m/z = 748.6 $[M+H]^+$, 90.89%.

Step 5. N-(3,3-Difluoro-1-methylcyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and N-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide



The compound was synthesized following the procedure described for the synthesis of Example 54, step 5, starting with a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-(3,3-difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropylbenzamide. The crude was purified by prep-HPLC (Method V) to obtain both regioisomers as solids.

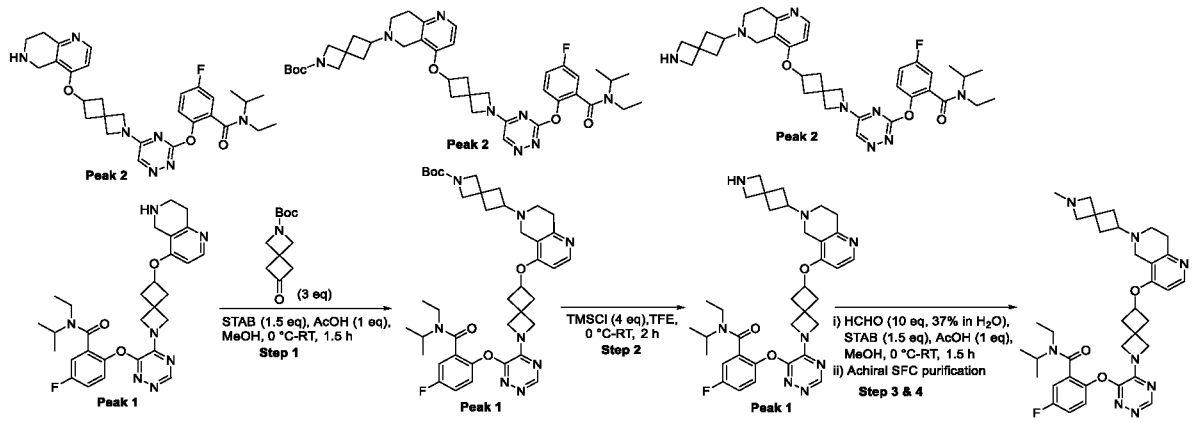
Peak 1. *N*-(3,3-Difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

Yield: 17.96%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 - 8.44 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.50 - 7.34 (m, 3H), 6.66 (d, J = 5.5 Hz, 1H), 4.81 - 4.71 (m, 1H), 4.69 - 4.51 (m, 2H), 4.29 - 4.09 (m, 2H), 3.71 (s, 2H), 3.47 - 3.34 (m, 2H), 3.17 - 2.98 (m, 2H), 2.95 (t, J = 5.6 Hz, 2H), 2.91 - 2.72 (m, 4H), 2.71 - 2.66 (m, 2H), 2.32 (d, J = 8.7 Hz, 2H), 1.44 (br s, 3H), 1.31 - 0.82 (m, 6H); LCMS (Method G): Rt = 1.73 min, m/z = 624.3 $[M+H]^+$; HPLC (Method D): Rt = 2.64 min, 97.23%.

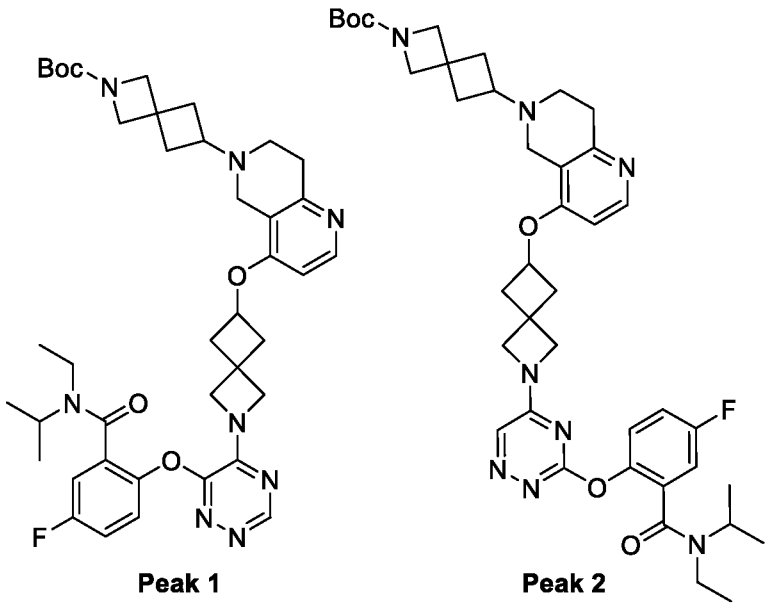
Peak 2. *N*-(3,3-Difluoro-1-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide.

Yield: 5.02%; LCMS (Method B): Rt = 1.35 min, m/z = 623.8 $[M+H]^+$, 98.19%.

Example 56. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 284)



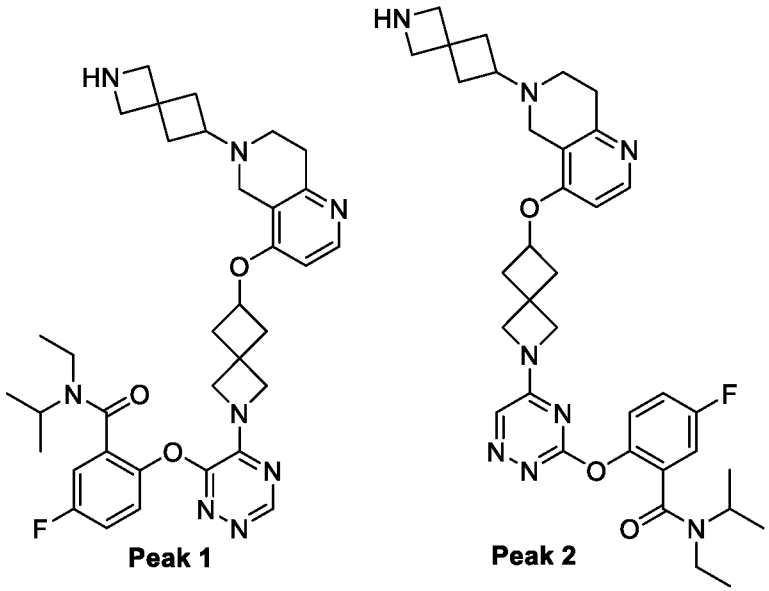
Step 1. tert-Butyl 6-(4-((2-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-azaspiro[3.3]heptane-2-carboxylate and tert-butyl 6-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-azaspiro[3.3]heptane-2-carboxylate



In a 25 mL two neck round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and the other regioisomer (500 mg, 0.913 mmol) was dissolved in MeOH (6 mL). To this solution, *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (579 mg, 2.74 mmol) and AcOH (0.052 mL, 0.913 mmol) were added at RT. The reaction was stirred at RT for 30 min. STAB (290 mg, 1.370 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was diluted with 10% $NaHCO_3$ (7 mL) and

the mixture was extracted with 10% MeOH in DCM (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified using silica gel flash chromatography using MeOH in DCM (product was eluted at 11% MeOH in DCM) to afford *tert*-butyl 6-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-azaspiro[3.3]heptane-2-carboxylate and the other regioisomer (678 mg, 84.24% yield). LCMS (Method G): Rt = 2.13 min, m/z = 743.4 $[M+H]^+$, 84.24%.

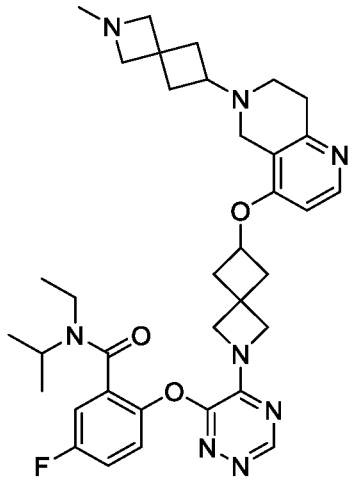
Step 2. 2-((5-(6-((6-(2-Azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-(2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



In a dried, 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 6-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-azaspiro[3.3]heptane-2-carboxylate and the other regioisomer (160 mg, 0.215 mmol) were added in TFE (6 mL). TMSCl (0.11 mL, 0.861 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with saturated $NaHCO_3$ solution (8 mL) and extracted with 10% MeOH in DCM (3 x 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was

concentrated under reduced pressure. The residue was triturated with MTBE (5 mL) and EtOAc (50 mL) to afford crude 2-((5-(6-((6-(2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer hydrochloride (102 mg, 70.5% yield). LCMS (Method G): Rt = 1.59 min, m/z = 643.6 $[M+H]^+$, 34.05%; 1.64 min, m/z = 643.6 $[M+H]^+$, 61.66%. This material was used without further purification.

Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



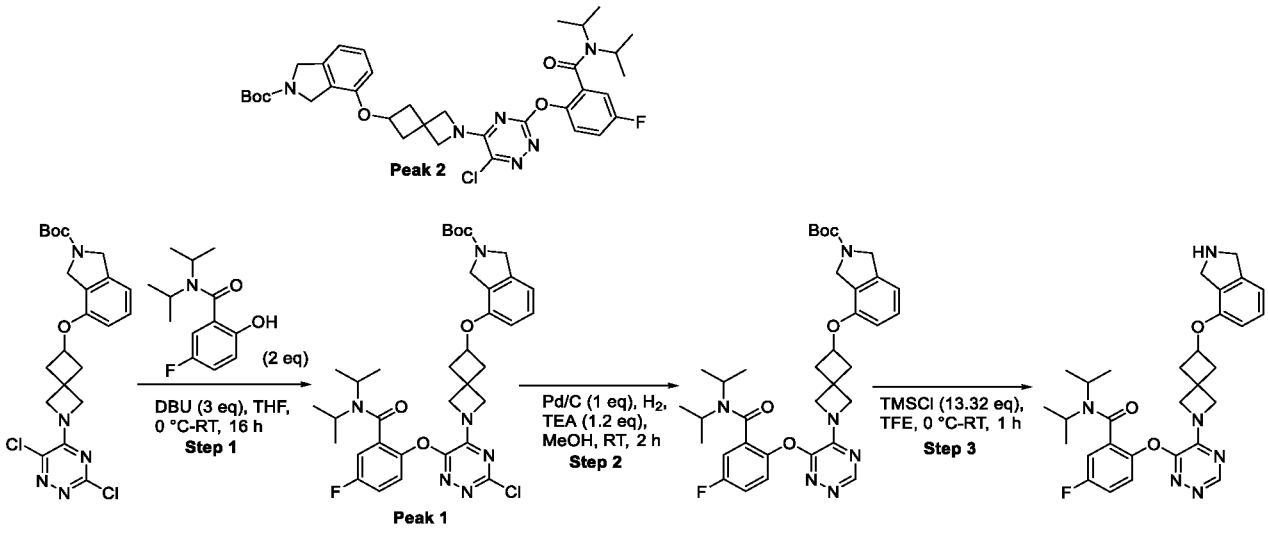
Step 3 was performed following the same procedure in two batches, 50 mg and 265 mg batches.

In a dried, 25 mL round bottom flask under a nitrogen atmosphere, 2-((5-(6-((6-(2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (265 mg, 0.412 mmol) was dissolved in MeOH (4 mL). To this solution, formaldehyde (0.114 mL, 4.12 mmol, 37 wt% in H_2O) and AcOH (0.024 mL, 0.412 mmol) were added at RT, and the reaction was stirred at RT for 20 min. STAB (131 mg, 0.618 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM, 4 drops of aq. ammonia). After completion, the reaction mixtures from both batches were combined and concentrated under reduced pressure. The crude compound was triturated with MTBE (3 x 5 mL). The resulting solid was diluted with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 8 mL). The combined organic layer was washed with brine solution (10 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep

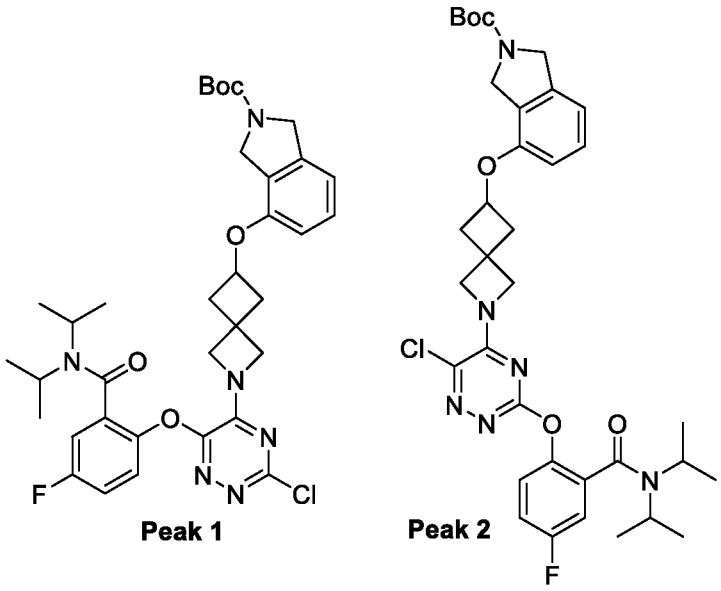
C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford a mixture of regioisomers. The regioisomers were purified by achiral Prep SFC (Method J) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (46 mg, 14.29% combined yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.40 - 7.31 (m, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.69 - 4.43 (m, 2H), 4.36 - 4.07 (m, 2H), 3.68 - 3.57 (m, 1H), 3.45 - 3.37 (m, 1H), 3.28 (br s, 2H), 3.18 - 2.93 (m, 6H), 2.89 - 2.72 (m, 5H), 2.40 - 2.19 (m, 5H), 2.15 (s, 3H), 1.99 - 1.85 (m, 2H), 1.22 - 0.61 (m, 9H); LCMS (Method G): Rt = 1.71 min, m/z = 657.4 $[M+H]^+$; HPLC (Method A): Rt = 4.12 min, 97.74%.

Note: Peak 2 was not isolated.

Example 57. 5-Fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*,*N*-diisopropylbenzamide (Compound No. 6)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



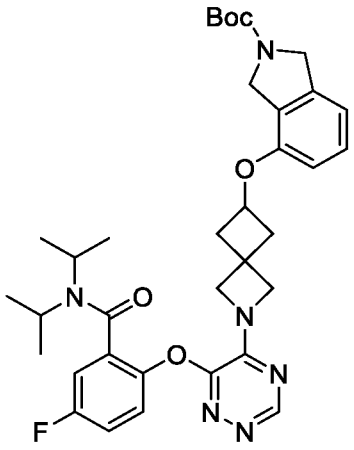
This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and 2 equivalents of 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide, except that 3 equivalents of DBU was used. The reaction was stirred at RT. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane to obtain both regioisomers (peak 1 eluted at 20% EtOAc in hexane and peak 2 eluted at 25% EtOAc in hexane).

Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate. Yield: 39.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 - 7.20 (m, 3H), 6.93 - 6.87 (m, 1H), 6.74 (d, J = 8.0 Hz, 1H), 4.78 - 4.61 (m, 3H), 4.59 - 4.47 (m, 4H), 4.30 - 4.18 (m, 2H), 3.61 - 3.43 (m, 2H), 2.85 - 2.76 (m, 2H), 1.49 - 1.38 (m, 12H), 1.34 - 1.25 (m, 3H), 1.11 - 0.99 (m, 3H), 0.73 (br d, J = 6.1 Hz, 3H), three protons merged with solvent peaks; LCMS (Method H): Rt = 2.61 min, m/z = 681.2 $[M+H]^+$; 93.20%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate.

Yield: 22.23%; LCMS (Method H): Rt = 2.64 min, m/z = 681.2 $[M+H]^+$; 92.18%.

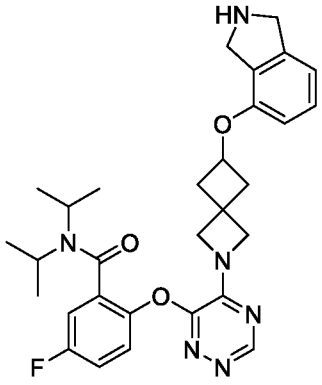
Step 2. tert-Butyl 4-((2-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 1 equivalent of Pd/C and 1.2 equivalents of Et_3N were used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 70% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate.

Yield: 78%; LCMS (Method H): Rt = 2.28 min, m/z = 647.2 $[M+H]^+$; 99.30%.

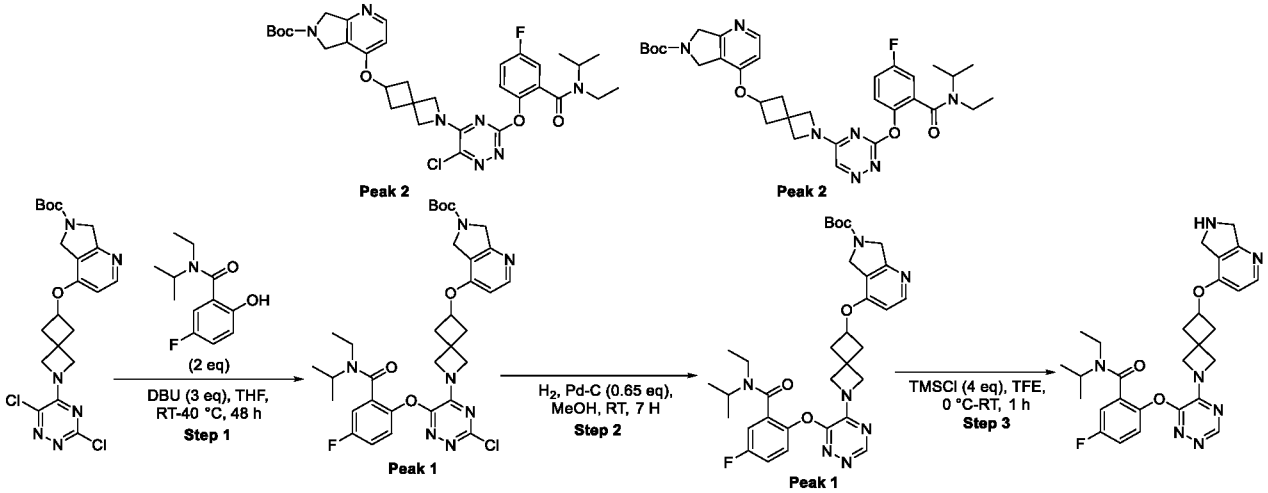
Step 3. 5-Fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N,N-diisopropylbenzamide



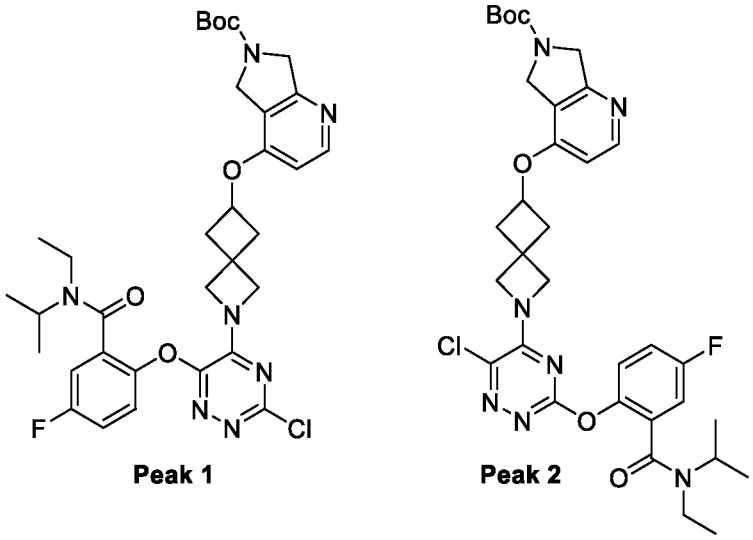
This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 13.32 equivalents of TMSCl was used. The reaction was concentrated under reduced pressure to obtain crude 5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*,*N*-diisopropylbenzamide hydrochloride.

The crude was purified by Prep HPLC (Method E). The fractions were concentrated under reduced pressure and lyophilized to obtain 5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*,*N*-diisopropylbenzamide as a solid. Yield: 71.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.44 (dd, *J* = 4.6, 8.9 Hz, 1H), 7.38 - 7.27 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.77 - 4.45 (m, 4H), 4.30 - 4.10 (m, 2H), 4.04 (s, 2H), 3.99 (s, 2H), 3.61 - 3.40 (m, 2H), 2.79 (br s, 2H), 2.32 - 2.17 (m, 2H), 1.42 (br s, 3H), 1.28 (d, *J* = 4.9 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H); LCMS (Method D): Rt = 1.73 min, m/z = 547.1 $[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 99.03%.

Example 58. 2-((5-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 285)



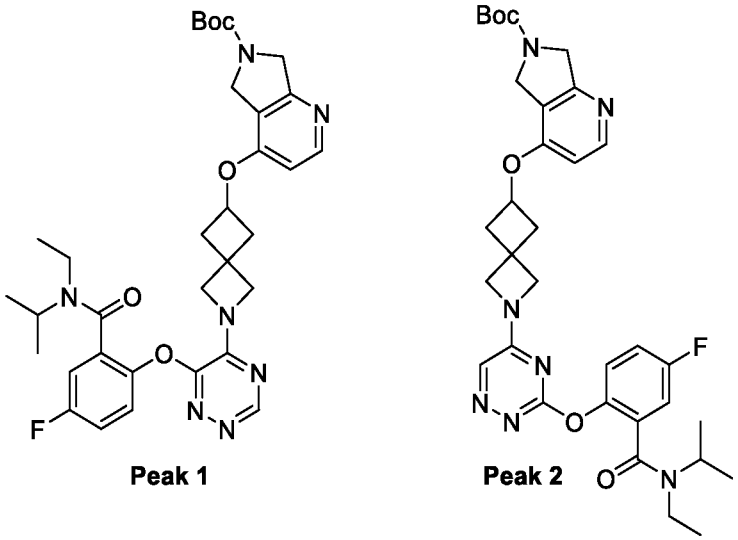
Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 2 equivalents of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and 3 equivalents of DBU were used. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 100% EtOAc) to obtain a mixture of regioisomers, *tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and *tert*-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a solid. This material was used without further purification of regioisomers.

Yield: 95%; LCMS (Method G): Rt = 2.27 min, m/z = 668.3 $[M+H]^+$, 95.02%.

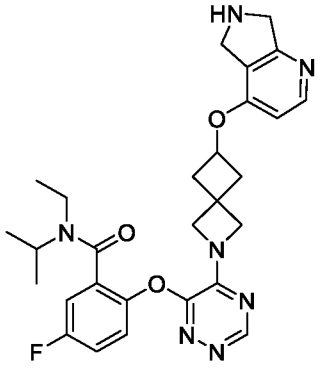
*Step 2. tert-Butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and tert-butyl 4-((*2-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with a mixture of *tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer, except that 0.65 equivalent of Pd-C was used. The crude was purified by silica gel flash column chromatography using methanol in DCM (product was eluted at 5-7% methanol in DCM) to obtain mixture of both isomers, *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and *tert*-butyl 4-((2-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a solid. This material was used without further purification of the regioisomers.

Yield: 44.3%; LCMS (Method G): Rt = 2.03 min, m/z = 634.6 $[M+H]^+$, 98.40%.

Step 3. 2-((5-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

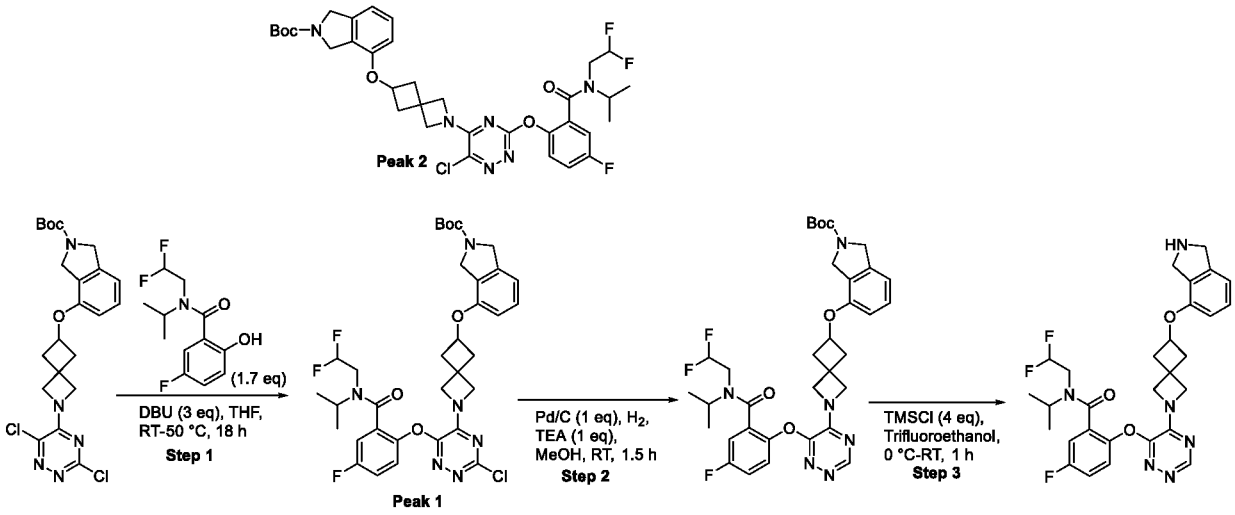


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with a mixture of *tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH), then by achiral SFC (Method L) to obtain 2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as solid.

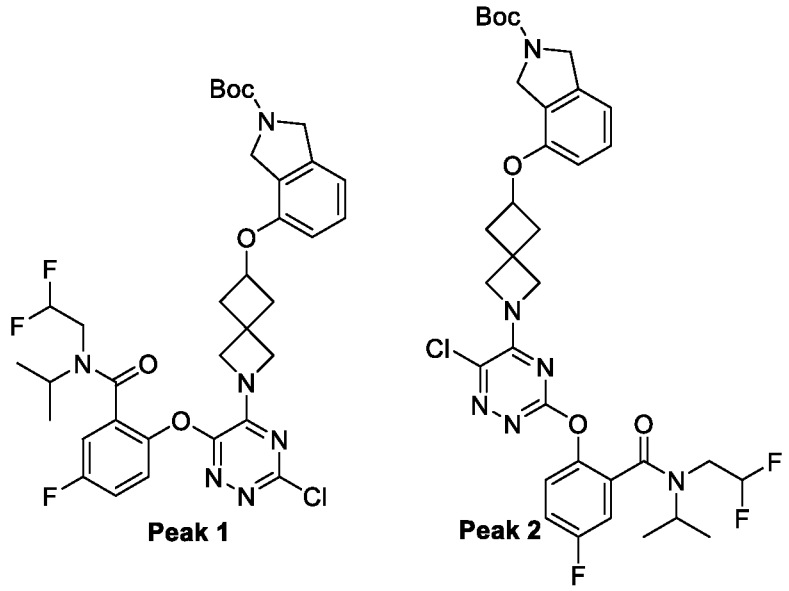
Yield: 94%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.23 (d, J = 5.8 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.33 (m, 2H), 6.71 (d, J = 5.8 Hz, 1H), 4.87 - 4.78 (m, 1H), 4.67 - 4.46 (m, 2H), 4.33 - 4.11 (m, 3H), 4.04 (br s, 2H), 4.00 (br s, 2H), 3.68 - 3.56 (m, 1H), 3.16 - 2.97 (m, 2H), 2.89 - 2.77 (m, 2H), 2.38 - 2.31 (m, 2H), 1.16 - 0.66 (m, 9H); LCMS (Method G): Rt = 1.56 min, m/z = 534.3 $[M+H]^+$; HPLC (Method A): Rt = 4.13 min, 99.73%.

Note: Peak 2 was not isolated.

Example 59. *N*-(2,2-Difluoroethyl)-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (Compound No. 11)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and, 1.7 equivalents of *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 3 equivalents of DBU was used. The reaction was stirred at 50 °C. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 15% EtOAc in hexane) to obtain both regioisomers.

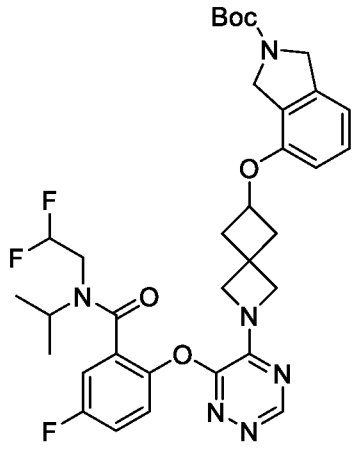
Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 36.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52 - 7.38 (m, 3H), 7.29 - 7.20 (m, 1H), 6.93 - 6.88 (m, 1H), 6.77 - 6.73 (m, 1H), 6.40 - 6.01 (m, 1H), 4.78 - 4.69 (m, 1H), 4.66 - 4.42 (m, 6H), 4.30 - 4.18 (m, 2H), 3.79 - 3.53 (m, 2H), 2.87 - 2.79 (m, 2H), 2.39 - 2.28 (m, 2H), 1.52 - 1.36 (m, 9H), 1.12 - 0.76 (m, 6H), one proton merged with solvent peak; LCMS (Method H): Rt = 2.51 min, m/z = 703.2 $[M+H]^+$; 92.99%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 18.34%; LCMS (Method H): Rt = 2.54 min, m/z = 703.1 $[M+H]^+$; 71.90%.

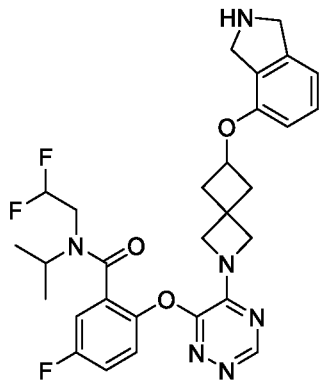
Step 2. tert-Butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 1 equivalent of Pd/C and 1 equivalent of Et_3N were used. After completion, the reaction was bubbled with nitrogen gas for 5 min. The reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 50% EtOAc in hexane) to obtain *tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 76%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.52 - 7.36 (m, 3H), 7.24 (t, J = 7.8 Hz, 1H), 6.90 (dd, J = 5.2, 7.2 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.39 - 5.98 (m, 1H), 4.80 - 4.68 (m, 1H), 4.61 - 4.42 (m, 6H), 4.27 - 4.09 (m, 2H), 3.81 - 3.50 (m, 2H), 2.85 - 2.75 (m, 2H), 2.38 - 2.28 (m, 2H), 1.46 (s, 9H), 1.10 - 0.68 (m, 6H), one proton merged with solvent peak; LCMS (Method D): Rt = 2.28 min, m/z = 669.2[M+H]$^+$; 87.91%.

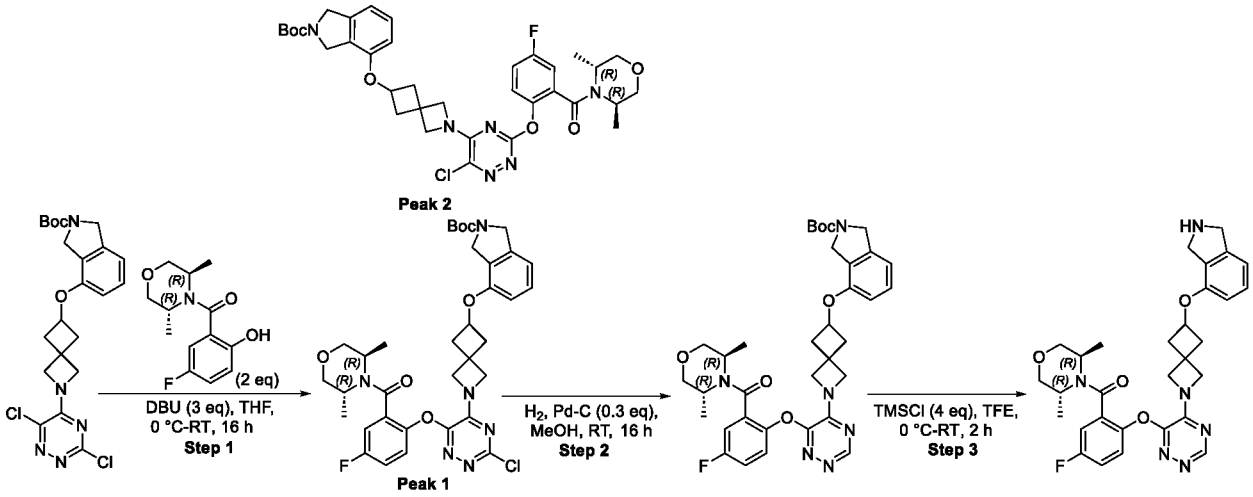
Step 3. N-(2,2-Difluoroethyl)-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide



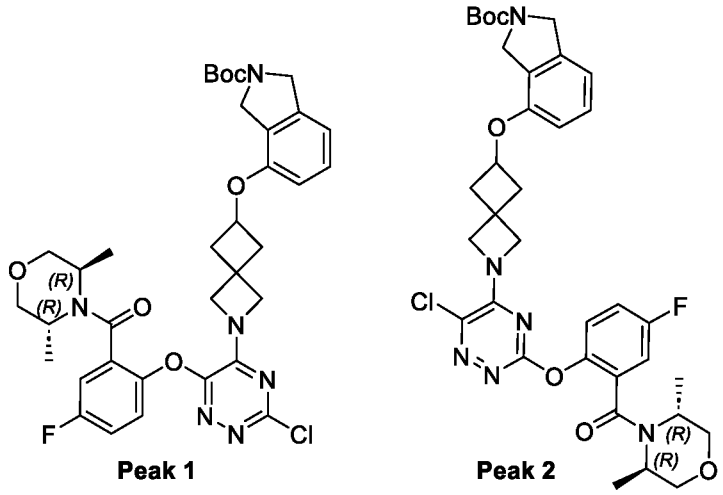
This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate. The reaction was concentrated under reduced pressure to obtain crude *N*-(2,2-difluoroethyl)-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide hydrochloride. The crude product was purified by Prep HPLC (Method AE) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 56.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.51 - 7.37 (m, 3H), 7.27 - 7.09 (m, 1H), 6.93 - 6.81 (m, 1H), 6.77 - 6.61 (m, 1H), 6.36 - 5.98 (m, 1H), 4.80 - 4.66 (m, 1H), 4.62 - 4.43 (m, 4H), 4.28 - 4.11 (m, 2H), 4.05 (s, 2H), 3.99 (s, 2H), 3.80 - 3.50 (m, 2H), 2.85 - 2.76 (m, 2H), 2.36 - 2.26 (m, 2H), 1.18 - 0.68 (m, 6H); LCMS (Method D): Rt = 1.75 min, m/z = 569.1 $[M+H]^+$; HPLC (Method A): Rt = 5.07 min, 99.60%.

Example 60. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (Compound No. 10)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-((3R,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((3R,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate

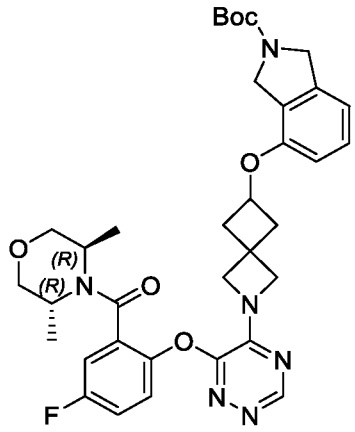


This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and 2 equivalents of (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone, except that 3 equivalents of DBU was used. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 100% EtOAc in hexane) to obtain peak 1 (less polar spot by TLC), *tert*-butyl 4-((2-(3-chloro-6-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 39.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 - 7.35 (m, 3H), 7.28 - 7.20 (m, 1H), 6.90 (t, J = 6.3 Hz, 1H), 6.78 - 6.70 (m, 1H), 4.83 - 4.60 (m, 3H), 4.57 (d, J = 10.1 Hz, 2H), 4.46 (t, J = 9.2 Hz, 2H), 4.31 (s, 1H), 4.24 (s, 1H), 3.69 (br s, 4H), 3.27 (br s, 2H), 2.89 - 2.72 (m, 2H), 2.40 - 2.23 (m, 2H), 1.50 - 1.42 (m, 9H), 1.18 - 1.10 (m, 6H); LCMS (Method D): Rt = 2.98 min, m/z = 695.1 $[M+H]^+$, 98.73%.

Note: Peak 2 was not isolated.

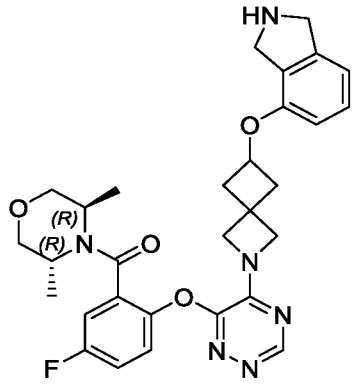
Step 2. tert-Butyl 4-((2-(6-(2-((3R,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 0.3 equivalent of Pd-C was used. The filtrate was concentrated under reduced pressure to crude obtain *tert*-butyl 4-((2-(6-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a semi-solid. This material was used without further purification.

Yield: 81%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 7.58 - 7.38 (m, 3H), 7.24 (t, J = 7.9 Hz, 1H), 6.94 - 6.89 (m, 1H), 6.75 (d, J = 8.2 Hz, 1H), 4.85 - 4.61 (m, 3H), 4.57 (d, J = 10.5 Hz, 2H), 4.50 - 4.30 (m, 4H), 4.25 - 3.23 (m, 6H), 2.92 - 2.74 (m, 2H), 2.43 - 2.27 (m, 2H), 1.45 (s, 9H), 1.22 - 1.08 (m, 6H); LCMS (Method D): Rt = 2.19 min, m/z = 661.1 $[M+H]^+$, 92.01%.

Step 3. ((3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone

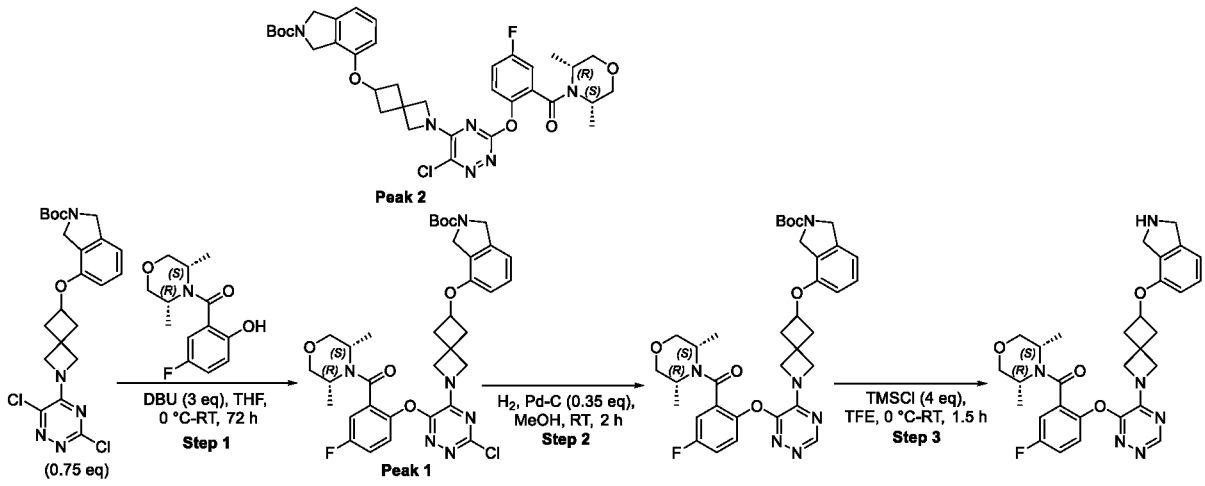


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-

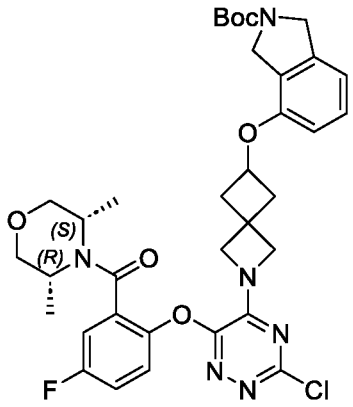
carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone hydrochloride. The crude was purified by Prep HPLC (Method AE) to obtain ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone as a solid.

Yield: 37.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (s, 1H), 7.50 - 7.36 (m, 4H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.77 - 4.66 (m, 1H), 4.68 - 4.39 (m, 4H), 4.37 - 4.09 (m, 2H), 4.04 (s, 2H), 3.98 (s, 2H), 3.68-3.65 (m, 3H), 2.91 - 2.70 (m, 3H), 2.53 - 2.52 (m, 2H), 1.17-1.11 (m, 6H); LCMS (Method D): Rt = 1.54 min, m/z = 561.3 [M+H]; HPLC (Method A): Rt = 4.59 min, 99.28%; Chiral SFC (Method Z): Rt = 4.36 min, 100%.

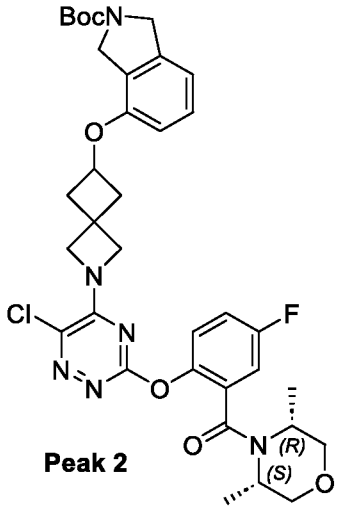
Example 61. ((*3S,5R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (Compound No. 39)



Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-((3S,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((3S,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



Peak 1



Peak 2

This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 0.75 equivalent of *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate and 1 equivalent of (3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone, except that 3 equivalents of DBU was used. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 48-60% EtOAc in hexane) to obtain both regioisomers.

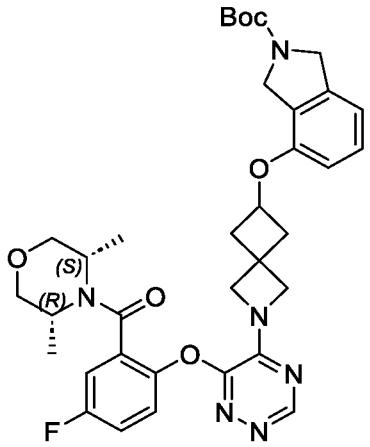
Peak 1 (less polar spot by TLC): *tert*-Butyl 4-((2-(3-chloro-6-(2-((*3S,5R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a semi-solid.

Yield: 18.07%; LCMS (Method D): Rt = 2.27 min, m/z = 695.6 $[M+H]^+$, 62.59%.

Peak 2 (more polar spot by TLC): *tert*-Butyl 4-((2-(6-chloro-3-(2-((*3S,5R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a semi-solid.

Yield: 6.09%; LCMS (Method D): Rt = 2.25 min, m/z = 695.6 $[M+H]^+$, 65.27%.

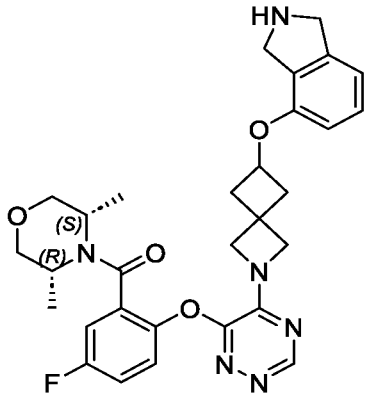
Step 2. tert-Butyl 4-((2-(6-(2-((3S,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-((3*S*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 0.35 equivalent Pd-C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(6-(2-((3*S*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 54.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 7.58 - 7.43 (m, 1H), 7.43 - 7.36 (m, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.94 - 6.87 (m, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.83 - 4.68 (m, 1H), 4.68 - 4.41 (m, 5H), 4.39 - 4.07 (m, 3H), 3.92 - 3.40 (m, 6H), 2.81-268 (m, 2H), 2.42 - 2.18 (m, 2H), 1.45 (s, 9H), 1.28 (br s, 6H); LCMS (Method D): Rt = 2.19 min, m/z = 661.3 $[M+H]^+$, 96.89%.

Step 3. ((3S,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone

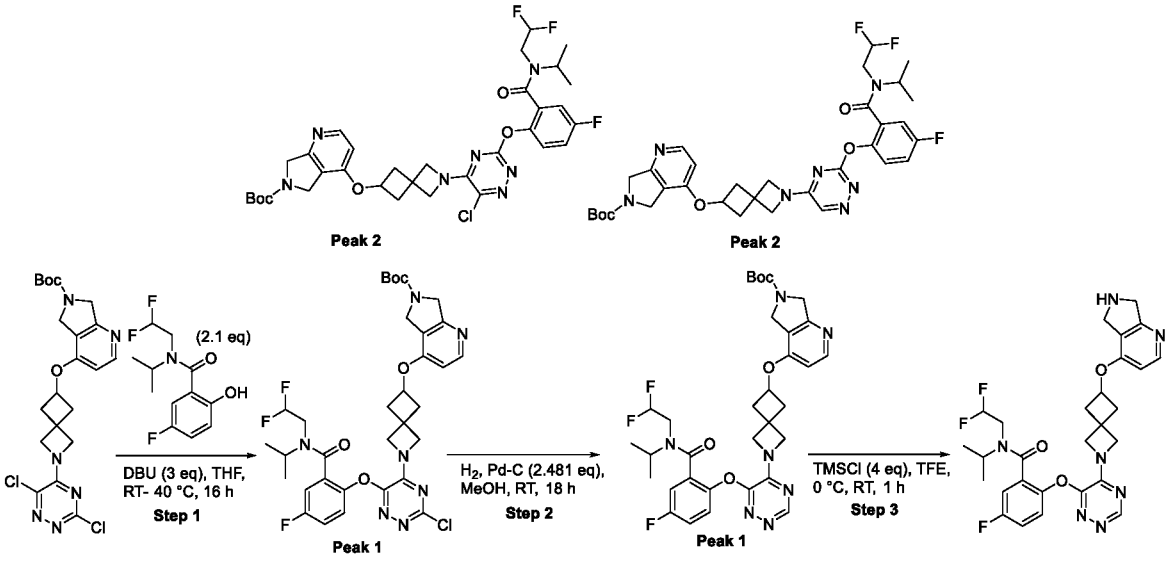


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with *tert*-butyl 4-((2-(6-(2-((3*S*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-

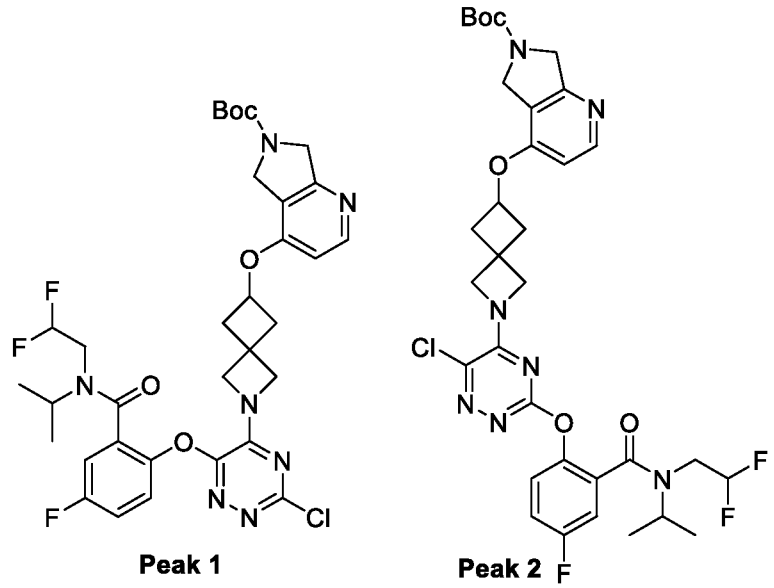
carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone hydrochloride. The crude was purified by Prep HPLC (Method F) to obtain (3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone as a solid.

Yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 7.54 - 7.42 (m, 2H), 7.42 - 7.33 (m, 1H), 7.23-7.10 (m, 1H), 6.90-6.82 (m, 1H), 6.75-6.63 (m, 1H), 4.80 - 4.65 (m, 1H), 4.57 - 4.47 (m, 2H), 4.25-4.18 (m, 2H), 4.04 (s, 2H), 3.99 (s, 2H), 3.82 - 3.10 (m, 6H), 2.81 (br s, 2H), 2.38 - 2.19 (m, 2H), 1.28 (br s, 6H); one protons merged with solvent peaks. LCMS (Method B): Rt = 1.69 min, m/z = 561.4 $[M+H]^+$; HPLC (Method A): Rt = 4.58 min, 99.88%; Chiral SFC (Method Q): Rt = 3.0 min, 99.27%.

Example 62. *N*-(2,2-Difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 311)



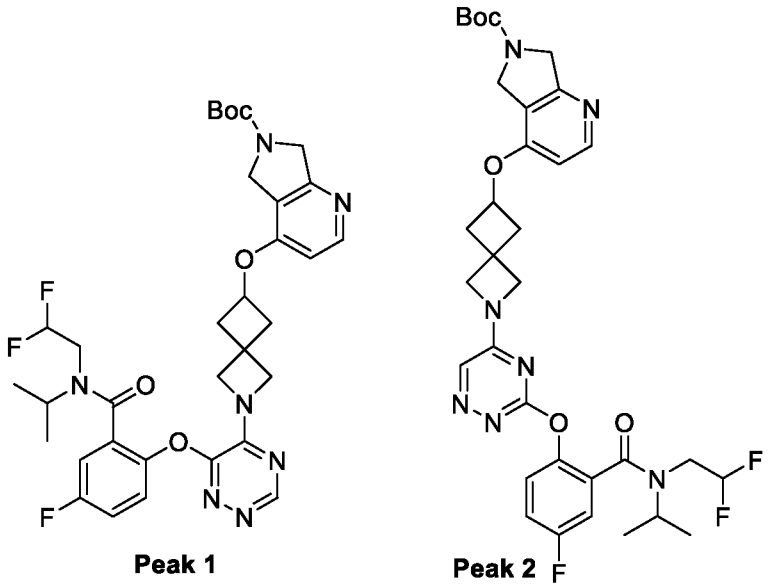
Step 1. tert-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and tert-butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 8, step 2, starting with *tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 2.1 equivalents of *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide was used. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80% EtOAc in hexane) to obtain mixture of *tert*-butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer . This mixture of regioisomers were used without further purification.

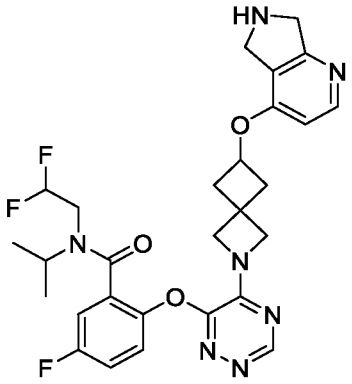
Yield: 85%; LCMS (Method G): Rt = 2.32 min, m/z = 704.2 $[M+H]^+$; 85.51%.

Step 2. tert-Butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and tert-butyl 4-((2-(3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 8, step 3, starting with *tert*-butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer, except that 2.48 equivalents of Pd/C was used in two lots (1.654 eq + 0.827 eq), and MeOH was used as a solvent. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain mixture of *tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer This mixture of regioisomers was used without further purification. Yield: 30.8%; LCMS (Method B): Rt = 1.78 min, m/z = 670.2 $[M+H]^+$; 60.99%

Step 3. N-(2,2-Difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 8, step 4, starting with *tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and the other regioisomer, except that 4 equivalents TMSCl was used. To this crude material, a saturated sodium bicarbonate solution was added, and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain a mixture of *N*-(2,2-difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide hydrochloride and other regioisomer. The crude was purified by Prep HPLC (Method Q). The fractions were concentrated under reduced pressure to obtain both regioisomers.

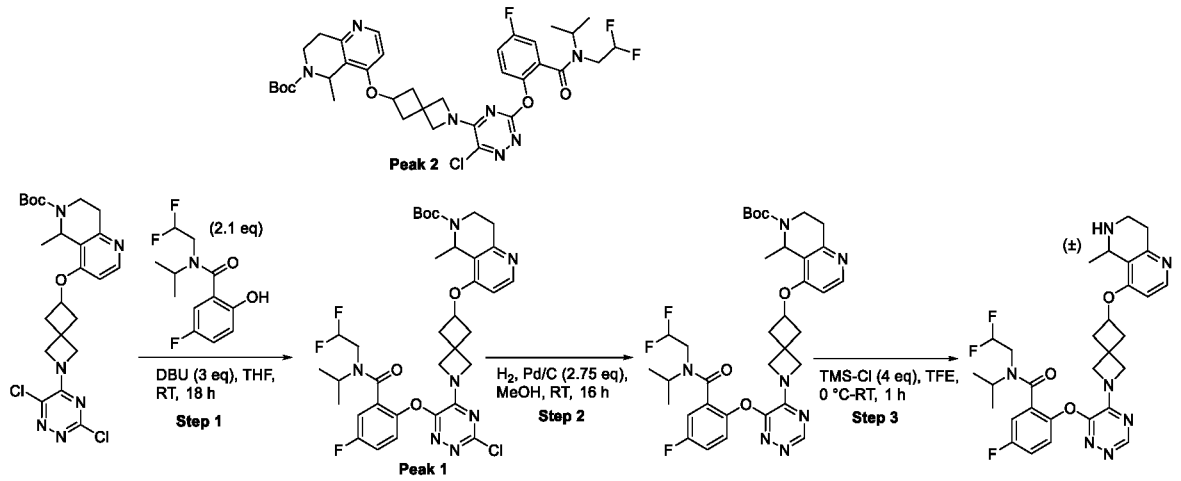
Peak 1 : Peak 1 was neutralized with saturated sodium bicarbonate solution and extracted with DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain *N*-(2,2-difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (HPLC: 68.79%). Then, it was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) and then by, Prep HPLC (Method C) to obtain *N*-(2,2-difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 33.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.23 (d, J = 5.5 Hz, 1H), 7.50 - 7.37 (m, 3H), 6.71 (d, J = 5.7 Hz, 1H), 6.35 - 6.01 (m, 1H), 4.91 - 4.75 (m, 1H), 4.63 - 4.41 (m, 3H), 4.30 - 4.12 (m, 2H), 4.04 (br s, 2H), 4.00 (s, 2H), 3.82 - 3.46 (m, 3H), 2.83 (br s,

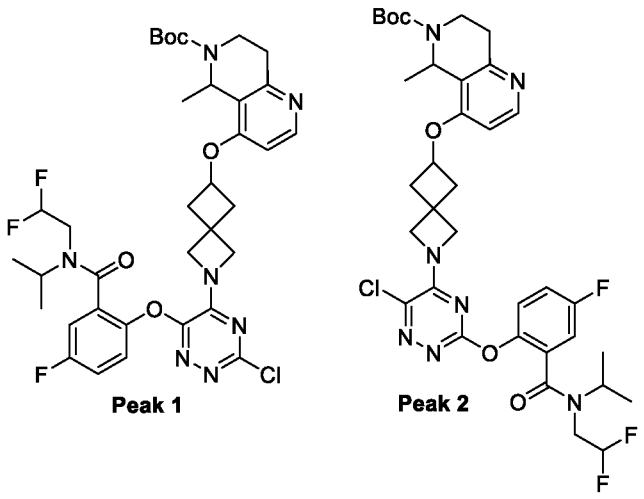
2H), 2.41 - 2.30 (m, 2H), 1.18 - 0.66 (m, 6H); LCMS (Method G): Rt = 1.56 min, m/z = 570.5 $[M+H]^+$; HPLC (Method A): Rt = 4.23 min, 99.75%.

Peak 2 : *N*-(2,2-Difluoroethyl)-2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid. Yield: 10.94%; LCMS (Method B): Rt = 1.34 min, m/z = 570.2 $[M+H]^+$; 65.34%.

Example 63. (±)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 202)



Step 1. (±)-tert-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and (±)-tert-butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of (±)-*tert*-butyl 4-((2-(3,6-dichloro-1,2,4-

triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and 2.1 equivalents of *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 3 equivalents of DBU was used. The reaction was stirred at RT. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 90% EtOAc in hexane) and then by achiral Prep SFC (Method D) to obtain both regioisomers.

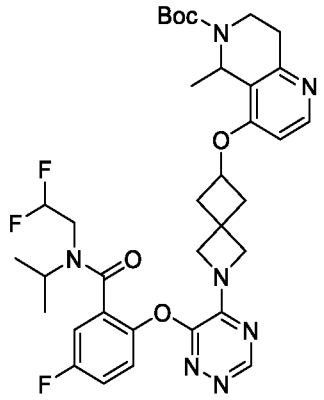
Peak 1. (±)-*tert*-Butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 21.28%; LCMS (Method B): Rt = 1.85 min, m/z = 732.1 $[M+H]^+$; 95.80%.

Peak 2. (±)-*tert*-Butyl 4-((2-(6-chloro-3-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 22.08%; LCMS (Method B): Rt = 1.93 min, m/z = 732.2 $[M+H]^+$; 99.43%.

Step 2. (±)-tert-Butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

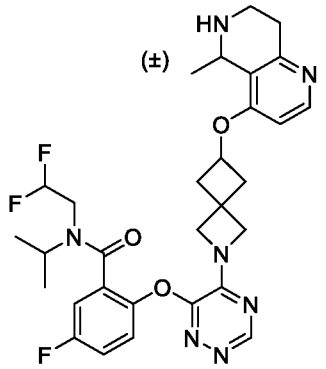


This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with of (±)-*tert*-butyl 4-((2-(3-chloro-6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 2.75 equivalents of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-

azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. This material was used without further purification.

Yield: 84%; ^{1}H NMR (400 MHz, DMSO): δ 8.62 (d, *J* = 6.5 Hz, 1H), 8.52 (s, 1H), 7.51 - 7.38 (m, 3H), 7.29 (d, *J* = 6.5 Hz, 1H), 6.41 - 5.99 (m, 1H), 5.35 - 5.03 (m, 2H), 4.73 - 4.51 (m, 2H), 4.34 - 4.03 (m, 3H), 3.85 - 3.68 (m, 2H), 3.63 - 3.31 (m, 4H), 3.04 - 2.87 (m, 4H), 1.49 - 1.34 (m, 12H), 1.19 - 0.68 (m, 6H); LCMS (Method G): Rt = 2.01 min, m/z = 698.6 $[M+H]^+$; 95.70%.

Step 3. (±)-*N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide*



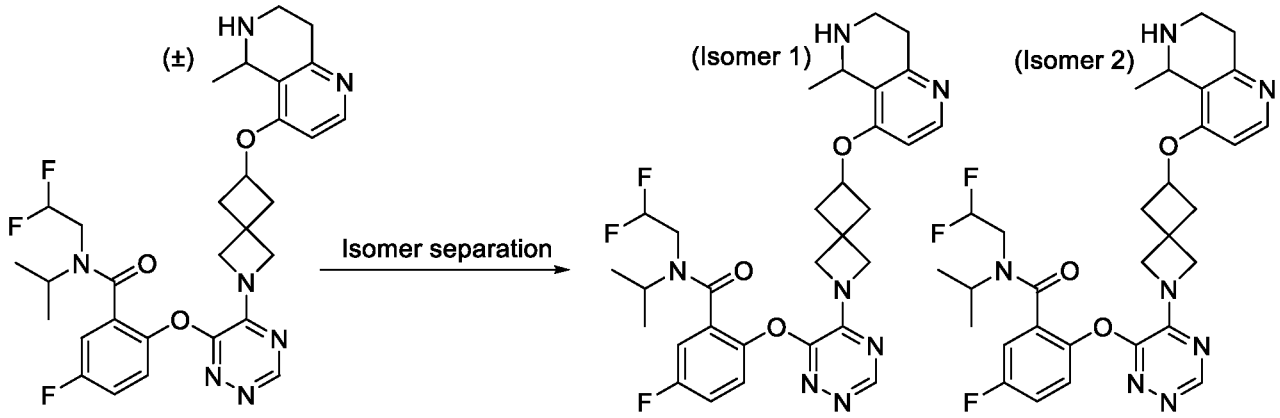
This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with (±)-*tert*-butyl 4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (±)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

Yield: 80%; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.46 (s, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.51 - 7.37 (m, 3H), 6.67 (d, *J* = 5.6 Hz, 1H), 6.37 - 5.98 (m, 1H), 4.82 - 4.75 (m, 1H), 4.66 - 4.41 (m, 2H), 4.32 - 4.13 (m, 2H), 4.07 (q, *J* = 6.2 Hz, 1H), 3.83 - 3.45 (m, 3H), 3.15 - 3.03 (m, 1H), 2.94 - 2.76 (m, 3H), 2.66 - 2.60 (m, 2H), 2.32 - 2.27 (m, 2H), 1.29 (br d, *J* = 5.6 Hz, 3H), 1.17 - 0.69 (m, 6H), one proton merged with solvent peaks. LCMS (Method D): Rt =

1.65 min, m/z = 598.3 $[M+H]^+$; HPLC (Method A): Rt = 4.73 min, 99.79%; Chiral SFC (Method J): Peak 1: Rt = 3.26 min, 49.34%; Peak 2: Rt = 3.95 min, 49.02%.

Example 64. (*E1*)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 210)

Example 65. (*E2*)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 211)



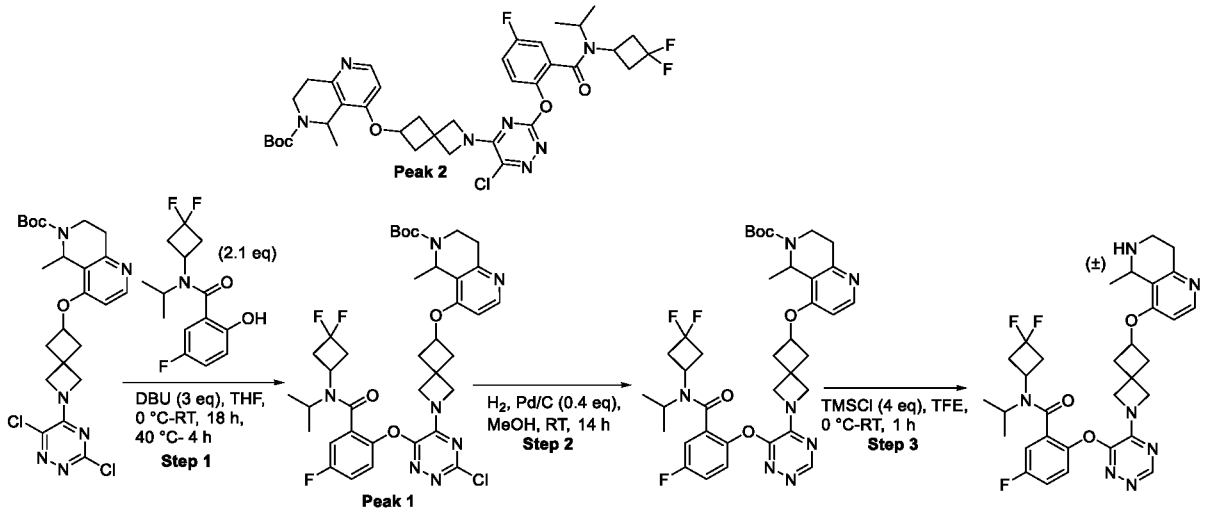
(±)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (133 mg, 0.223 mmol) was purified by chiral SFC (Method C) to obtain (*E1*)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (29 mg, 21.71% yield) and (*E2*)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (45 mg, 33.6% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.52 - 7.36 (m, 3H), 6.67 (d, J = 5.5 Hz, 1H), 6.37 - 5.98 (m, 1H), 4.84 - 4.71 (m, 1H), 4.66 - 4.43 (m, 2H), 4.32 - 4.13 (m, 2H), 4.07 (q, J = 6.0 Hz, 1H), 3.80 - 3.45 (m, 3H), 3.13 - 3.02 (m, 1H), 2.95 - 2.78 (m, 3H), 2.74 - 2.59 (m, 2H), 2.33 - 2.27 (m, 2H), 1.30 (br d, J = 5.6 Hz, 3H), 1.17 - 0.67 (m, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.60 min, m/z = 598.2 $[M+H]^+$; HPLC (Method A): Rt = 4.79 min, 99.55%; Chiral SFC (Method J): Rt = 3.32 min, 99.46%.

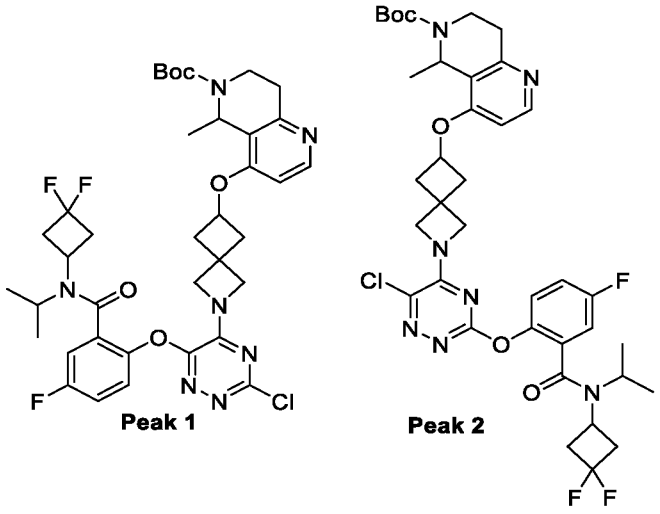
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.52 - 7.37 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 6.38 - 5.97 (m, 1H), 4.84 - 4.70 (m, 1H), 4.65 - 4.42 (m, 2H), 4.28 - 4.13 (m, 2H), 4.09 (q, J = 6.1 Hz, 1H), 3.83 - 3.47 (m, 3H), 3.13 - 3.04 (m,

1H), 2.96 - 2.79 (m, 3H), 2.75 - 2.60 (m, 2H), 2.33 - 2.25 (m, 2H), 1.30 (br d, *J* = 5.6 Hz, 3H), 1.18 - 0.69 (m, 6H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.60 min, m/z = 598.2 $[M+H]^+$; HPLC (Method A): Rt = 4.79 min, 99.17%; Chiral SFC (Method J): RT = 4.04 min, 98.94%.

Example 66. (±)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 238)



Step 1. (±)- tert-Butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and (±)-tert-butyl 4-((2-(6-chloro-3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of (±)-*tert*-butyl 4-((2-(3,6-dichloro-1,2,4-

triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and 2.1 equivalents of *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 3 equivalents of DBU was used. The reaction was stirred at RT-40 °C. After the work-up, the crude product was purified by silica-gel column chromatography using MeOH in DCM (mixture of products were eluted at 5% MeOH in DCM), then by achiral Prep SFC (Method F) to obtain both regioisomers.

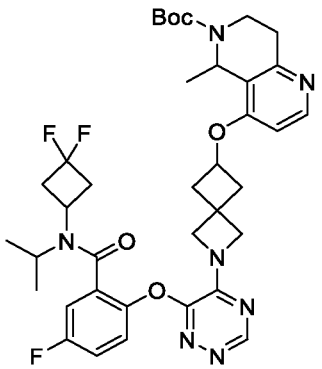
Peak 1. (±)-*tert*-Butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 35.7%; LCMS (Method B): Rt = 2.04 min, m/z = 758.2 $[M+H]^+$, 86.36%.

Peak 2. (±)-*tert*-Butyl 4-((2-(6-chloro-3-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

Yield: 22.09%; LCMS (Method G): Rt = 2.39 min, m/z = 758.6 $[M+H]^+$, 89.14%.

Step 2. (±)-tert-Butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



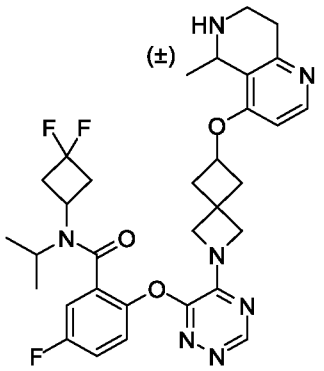
This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with (±)-*tert*-butyl 4-((2-(3-chloro-6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 0.4 equivalent of Pd/C was used.

The reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to afford crude (±)-*tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-

azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. This material was used without further purification.

Yield: 78%; LCMS (Method D): Rt = 2.55 min, m/z = 724.4 $[M+H]^+$; 79.03%.

Step 3. (±)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

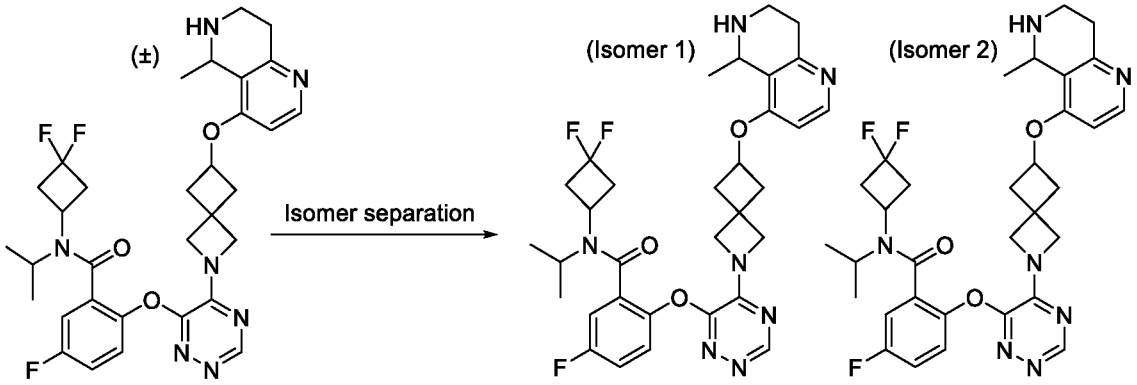


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with (±)-*tert*-butyl 4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (±)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 69.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.51 - 7.34 (m, 3H), 6.65 (br s, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.68 - 4.48 (m, 2H), 4.29 - 4.13 (m, 2H), 4.09 - 4.04 (m, 1H), 3.90 - 3.39 (m, 3H), 3.14 - 3.02 (m, 1H), 2.93 - 2.79 (m, 4H), 2.74 - 2.60 (m, 4H), 2.3 - 2.31 (m, 1H), 1.29 (d, J = 5.5 Hz, 3H), 1.19 - 0.58 (m, 6H), two protons merged with solvent peak; LCMS (Method A): Rt = 2.15 min, m/z = 624.3 $[M+H]^+$; HPLC (Method A): Rt = 5.07 min, 99.62%; Chiral SFC (Method AF): Peak 1: Rt = 8.39 min, 50.28%; Peak 2: Rt = 10.82 min, 49.17%.

Example 67. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 263)

Example 68. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 264)



(±)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (285 mg, 0.457 mmol) was purified by chiral Prep SFC (Method F) to afford both isomers, (*E1*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (99 mg, 34.5% yield) and (*E2*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (104 mg, 36.4% yield) as solids.

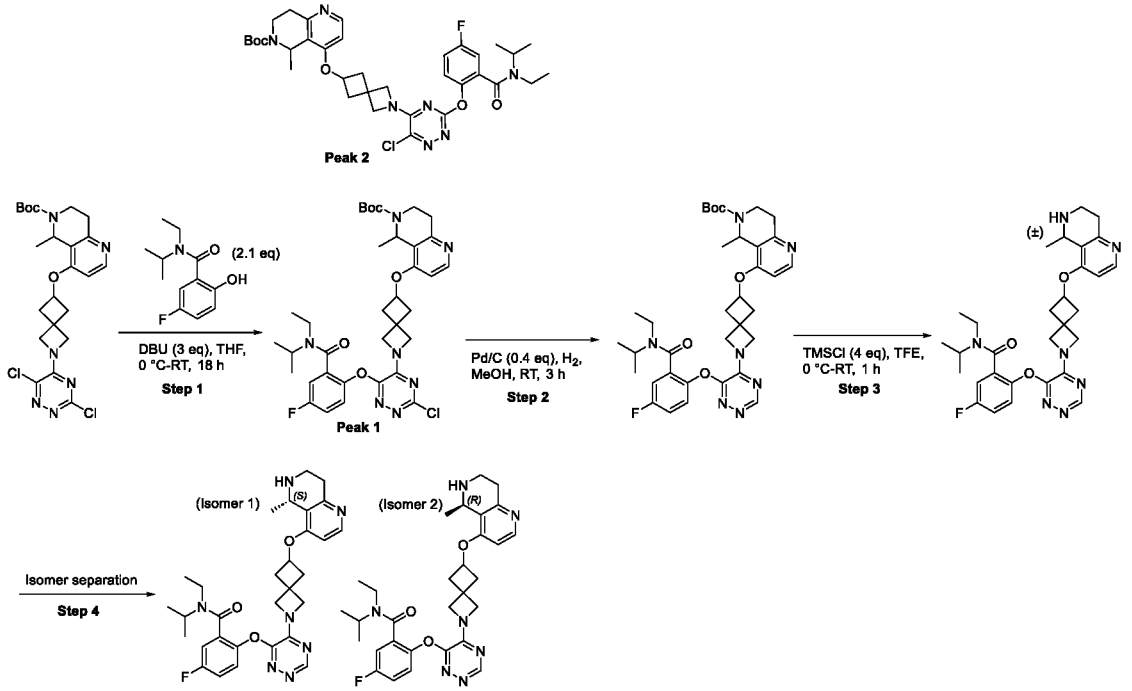
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.50 - 7.34 (m, 3H), 6.65 (br s, 1H), 4.78 (quin, J = 6.7 Hz, 1H), 4.67 - 4.51 (m, 2H), 4.31 - 4.15 (m, 2H), 4.10 - 4.03 (m, 1H), 3.90 - 3.55 (m, 3H), 3.13 - 3.03 (m, 1H), 2.93 - 2.77 (m, 4H), 2.73 - 2.63 (m, 4H), 2.33 - 2.30 (m, 1H), 1.29 (d, J = 5.8 Hz, 3H), 1.17 - 0.62 (m, 6H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.81 min, m/z = 624.5 $[M+H]^+$; HPLC (Method A): Rt = 5.19 min, 99.10%; Chiral SFC (Method AF): Rt = 9.27 min, 99.74%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.50 - 7.35 (m, 3H), 6.65 (br s, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.67 - 4.51 (m, 2H), 4.30 - 4.15 (m, 2H), 4.06 (q, J = 6.1 Hz, 1H), 3.91 - 3.56 (m, 3H), 3.12 - 3.04 (m, 1H), 2.96 - 2.77 (m, 4H), 2.75 - 2.58 (m, 4H), 2.23 (br s, 1H), 1.29 (d, J = 5.8 Hz, 3H), 1.17 - 0.64 (m, 6H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.79 min, m/z = 624.5 $[M+H]^+$;

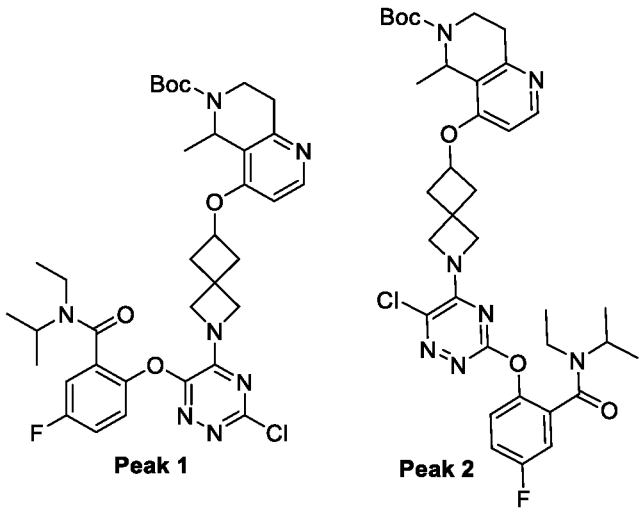
HPLC (Method A): Rt = 5.19 min, 99.39%; Chiral SFC (Method AF): Rt = 11.87 min, 97.84%.

Example 69. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 190)

Example 70. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 191)



Step 1. (±)-tert-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and (±)-tert-butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 2.1 equivalents of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 1 equivalent of (±)-*tert*-butyl 4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 3 equivalents of DBU was used. The reaction was stirred at RT. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 80% EtOAc in hexane) to obtain both regioisomers.

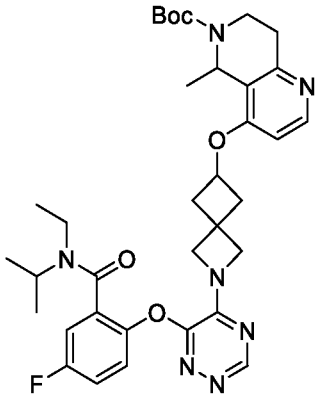
Peak 1 (less polar spot by TLC): (±)-*tert*-Butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 18.59%; LCMS (Method G): Rt = 2.21 min, m/z = 696.6 $[M+H]^+$; 94.04%.

Peak 2 (more polar spot by TLC): (±)-*tert*-Butyl 4-((2-(6-chloro-3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 8.89%; LCMS (Method B): Rt = 1.91 min, m/z = 696.0 $[M+H]^+$; 75.72%.

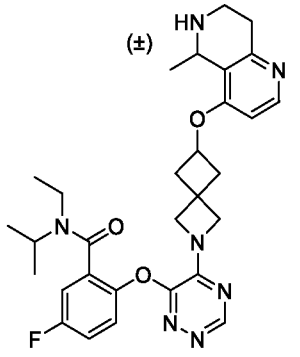
Step 2. (±)-tert-Butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 5, step 2, starting with (±)-*tert*-butyl 4-((2-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 0.4 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to afford crude (±)-*tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid. This material was used without further purification.

Yield: 58.6%; LCMS (Method D): Rt = 2.09 min, m/z = 662.4 $[M+H]^+$; 68.53%.

Step 3. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

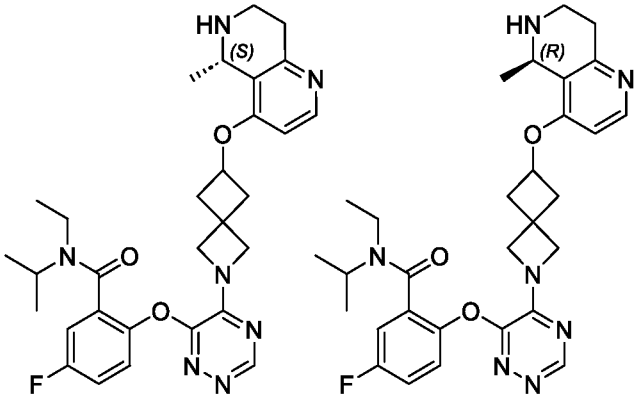


This compound was synthesized following the procedure described for the synthesis of Example 5, step 3, starting with (±)-*tert*-butyl 4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-

yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 58.6; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 - 8.43 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.49 - 7.31 (m, 3H), 6.66 (d, J = 5.6 Hz, 1H), 4.78 (quin, J = 6.5 Hz, 1H), 4.66 - 4.50 (m, 2H), 4.31 - 4.13 (m, 2H), 4.07 (q, J = 6.4 Hz, 1H), 3.67 - 3.57 (m, 1H), 3.46 - 3.38 (m, 1H), 3.16 - 2.97 (m, 3H), 2.96 - 2.77 (m, 3H), 2.71 - 2.59 (m, 2H), 2.33 - 2.22 (m, 2H), 1.29 (br d, J = 5.9 Hz, 3H), 0.68 - 1.15 (m, 9H); LCMS (Method D): Rt = 1.59 min, m/z = 562.4 $[M+H]^+$; HPLC (Method E): Rt = 2.98 min, 96.53%; Chiral SFC (Method J): Peak 1: Rt = 3.96 min, 50.06%; Peak 2: Rt = 4.99 min, 49.33%.

Step 4. (E1)-N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and (E2)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



(±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (67 mg, 0.119 mmol) was purified using chiral Prep SFC (Method C) to obtain both isomers, (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (11 mg, 16.21% yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (18 mg, 26.8% yield) as solids.

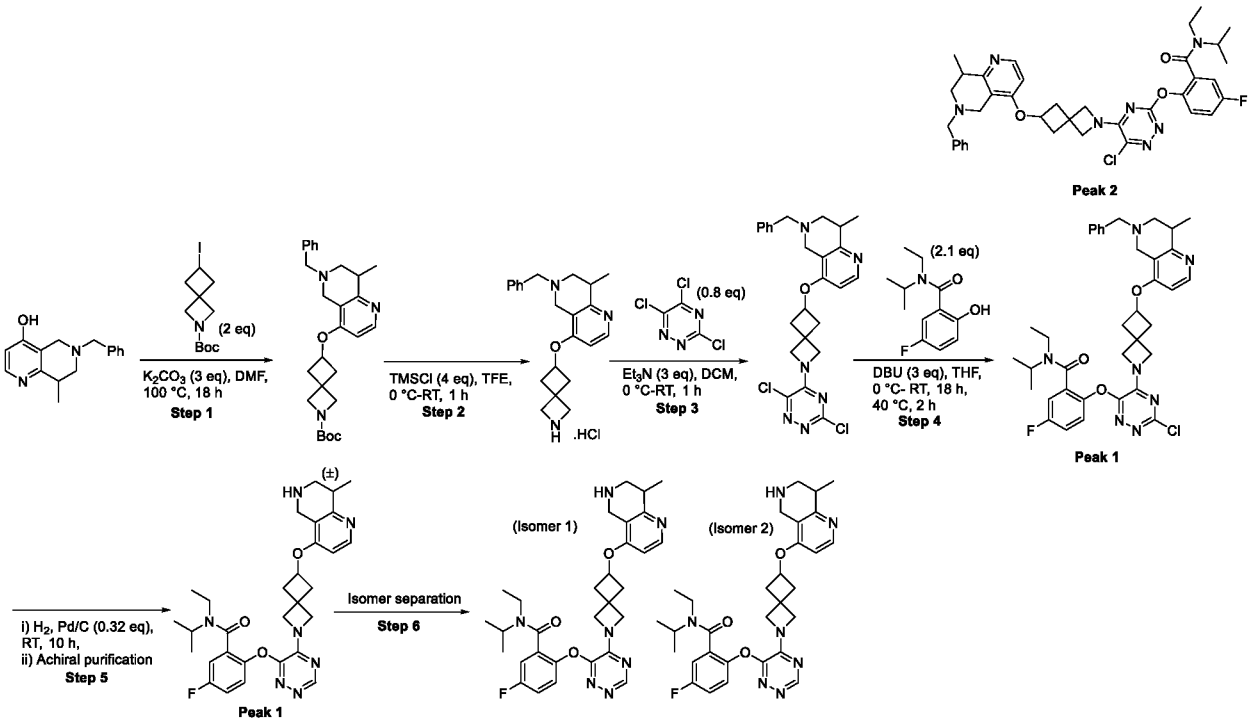
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 4.78 (quin, J = 6.5 Hz, 1H), 4.69 - 4.48 (m, 2H), 4.32

- 4.13 (m, 2H), 4.09 (q, *J* = 6.4 Hz, 1H), 3.69 - 3.56 (m, 1H), 3.45 - 3.36 (m, 1H), 3.15 - 2.99 (m, 3H), 2.96 - 2.78 (m, 3H), 2.73 - 2.61 (m, 2H), 2.32 - 2.20 (m, 2H), 1.30 (br d, *J* = 6.0 Hz, 3H), 1.15 - 0.68 (m, 9H); LCMS (Method D): Rt = 1.57 min, m/z = 562.3 $[M+H]^+$; HPLC (Method A): Rt = 4.31 min, 98.70%; Chiral SFC (Method J): Rt = 4.20 min, 99.05%.

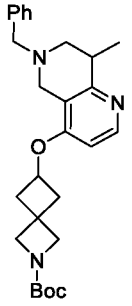
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.22 (d, *J* = 5.5 Hz, 1H), 7.48 - 7.32 (m, 3H), 6.71 (d, *J* = 5.5 Hz, 1H), 4.84 - 4.76 (m, 1H), 4.65 - 4.50 (m, 2H), 4.29 - 4.14 (m, 3H), 3.65 - 3.50 (m, 1H), 3.46 - 3.38 (m, 1H), 3.22 - 3.00 (m, 3H), 2.90 - 2.72 (m, 3H), 2.71 - 2.63 (m, 2H), 2.34 - 2.27 (m, 2H), 1.35 (br d, *J* = 6.3 Hz, 3H), 1.15 - 0.66 (m, 9H); LCMS (Method D): Rt = 1.57 min, m/z = 562.4 $[M+H]^+$; HPLC (Method A): Rt = 4.33 min, 99.82%; Chiral SFC (Method J): Rt = 5.54 min, 99.51%.

Example 71. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 290)

Example 72. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 291)

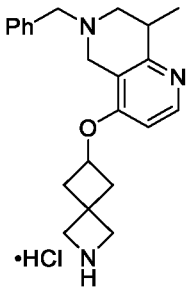


Step 1. (±)-tert-Butyl 6-((6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.2 g, 4.72 mmol) in DMF (10 mL), powdered K_2CO_3 (1.956 g, 14.15 mmol) was added at RT. The reaction was stirred at RT for 10 min. To this reaction mixture, *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (3.05 g, 9.44 mmol) was added, and the reaction was stirred at 100 °C for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was quenched with water (50 mL), and the reaction was extracted with DCM (2 x 100 mL). The combined organic layer was washed with ice-cold water (3 x 50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6-7% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (2 g, 84% yield). LCMS (Method G): Rt = 2.40 min, m/z = 450.4 $[M+H]^+$; 89.45%.

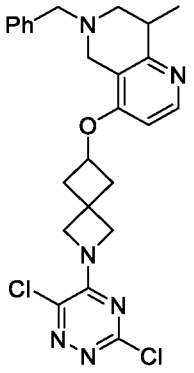
Step 2. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



To a stirred solution of (±)-*tert*-butyl 6-((6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (2 g, 4.45 mmol) in 2,2,2-trifluoroethanol (20 mL), TMSCl (2.274 mL, 17.79 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in EtOAc). After completion, the reaction was concentrated under reduced pressure. The crude was triturated with EtOAc (2 x 20 mL), decanted the layer and the solid was dried under vacuum to obtain (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-8-methyl-5,6,7,8-

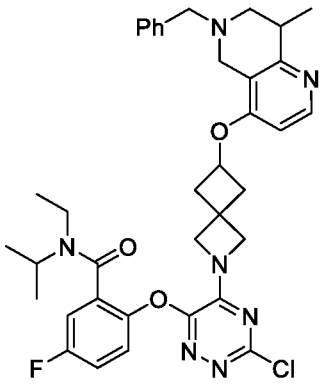
tetrahydro-1,6-naphthyridine hydrochloride (1.8 g, 93% yield). LCMS (Method G): Rt = 1.63 min, m/z = 350.3 $[M+H]^+$; 89.19%.

Step 3. (±)-6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine

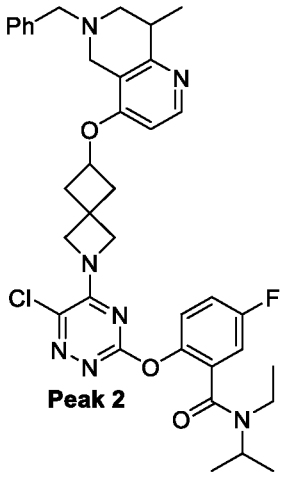


To a stirred solution of 3,5,6-trichloro-1,2,4-triazine (0.688 g, 3.73 mmol) in DCM (20 mL), TEA (1.950 mL, 13.99 mmol) was added at 0 °C under nitrogen atmosphere. To this reaction mixture, (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (1.8 g, 4.66 mmol) was added in DCM (5 mL). The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (100% EtOAc). The reaction was quenched with water (30 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 90% EtOAc in hexane) to obtain (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (700 mg, 28.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 5.5 Hz, 1H), 7.40 - 7.25 (m, 5H), 6.67 (d, J = 5.6 Hz, 1H), 4.83 - 4.68 (m, 3H), 4.27 - 4.12 (m, 2H), 3.75 - 3.62 (m, 2H), 3.47 (br s, 2H), 2.94 - 2.73 (m, 4H), 2.45 - 2.39 (m, 1H), 2.33 - 2.24 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H); LCMS (Method B): Rt = 1.53 min, m/z = 497.2 $[M+H]^+$; 94.61%.

Step 4. (±)-2-((5-(6-((6-Benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



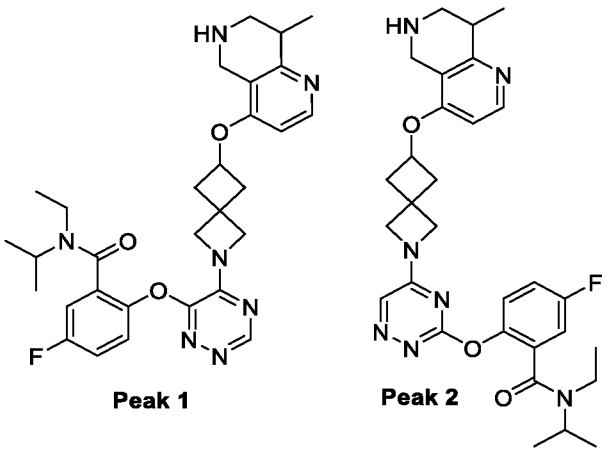
Peak 1



Peak 2

To a stirred solution of (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (700 mg, 1.407 mmol) in THF (10 mL), *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (666 mg, 2.96 mmol) and DBU (0.636 mL, 4.22 mmol) were added at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 18 h, then at 40 °C for 2 h. The reaction was monitored by TLC (100% EtOAc). The reaction was quenched with water (30 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 4% MeOH in DCM) to obtain (±)-2-((5-(6-((6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (830 mg, 79% yield). LCMS (Method G): Rt = 2.59 min, m/z = 686.3 $[M+H]^+$; 91.61%. This mixture of regioisomers were used without further purification.

Step 5. (±)-*N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and* (±)-*N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide*

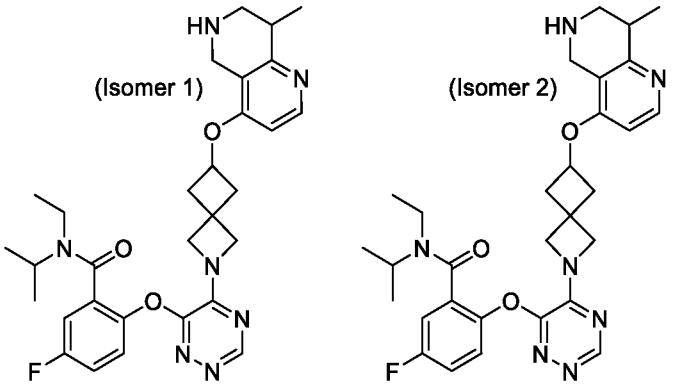


In a 100 mL round bottom flask, (±)-2-((5-(6-((6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (830 mg, 1.210 mmol) was added in 2,2,2-triflouroethanol (20 mL), and the solution was degassed with nitrogen for 2 min. Pd-C (415 mg, 0.390 mmol) was added to this solution, and the reaction was stirred at RT for 10 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (2 x 50 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain a mixture of regioisomers. The mixture of regioisomers was purified by achiral Prep SFC (Method G) to afford both regioisomers.

Peak 1. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide Yield: (180 mg, 26.1% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.22 (d, J = 5.4 Hz, 1H), 7.49 - 7.30 (m, 3H), 6.66 (d, J = 5.5 Hz, 1H), 4.76 (quin, J = 6.6 Hz, 1H), 4.67 - 4.48 (m, 2H), 4.33 - 4.08 (m, 2H), 3.72 (s, 2H), 3.67 - 3.55 (m, 1H), 3.48 - 3.37 (m, 1H), 3.13 - 2.97 (m, 3H), 2.89 - 2.62 (m, 5H), 2.33 - 2.30 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.17 - 0.65 (m, 9H); LCMS (Method G): Rt = 1.69 min, m/z = 562.2 $[M+H]^+$; HPLC (Method A): Rt = 4.61 min, 98.52%. Chiral SFC (Method AG): Peak 1: Rt = 3.23 min, 48.54%; Peak 2: Rt = 3.78 min, 49.63%.

Peak 2. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide (130 mg,18.55% yield). LCMS (Method B): Rt = 1.12 min, m/z = 562.2 $[M+H]^+$; HPLC (Method A): Rt = 4.72 min, 96.91%.

Step 6. (E1)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and (E2)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



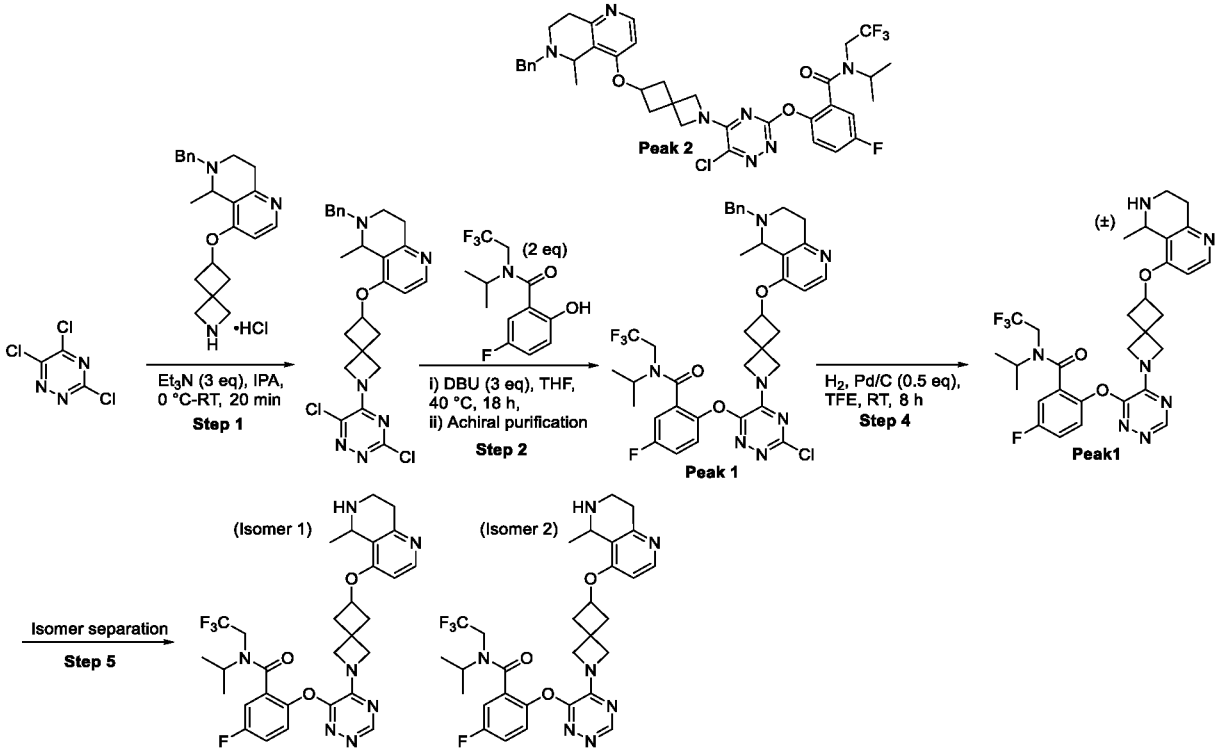
(±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (180 mg, 0.320 mmol) was purified by chiral Prep SFC (Method G). The fractions were concentrated under reduced pressure and lyophilized to obtain (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (43 mg, 22.96% yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (59 mg, 32.1% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.24 (d, J = 5.5 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 4.77 (quin, J = 6.6 Hz, 1H), 4.66 - 4.50 (m, 2H), 4.31 - 4.10 (m, 2H), 3.75 (s, 2H), 3.68 - 3.58 (m, 1H), 3.48 - 3.39 (m, 1H), 3.16 - 2.98 (m, 3H), 2.89 - 2.67 (m, 5H), 2.35 - 2.24 (m, 1H), 1.23 (d, J = 6.9 Hz, 3H), 1.17 - 0.66 (m, 9H); LCMS (Method G): Rt = 1.65 min, m/z = 562.4 $[M+H]^+$; HPLC (Method A): Rt = 4.55 min, 98.08%; Chiral SFC (Method AG): Rt = 3.18 min, 100%.

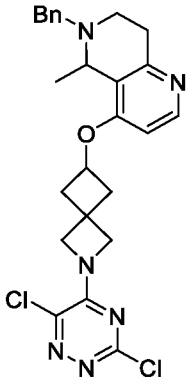
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.48 - 7.32 (m, 3H), 6.65 (d, J = 5.6 Hz, 1H), 4.76 (quin, J = 6.6 Hz, 1H), 4.65 - 4.49 (m, 2H), 4.30 - 4.12 (m, 2H), 3.71 (s, 2H), 3.67 - 3.57 (m, 1H), 3.47 - 3.38 (m, 1H), 3.15 - 3.00 (m, 3H), 2.88 - 2.60 (m, 5H), 2.36 - 2.23 (m, 1H), 1.22 (d, J = 6.9 Hz, 3H), 1.16 - 0.67 (m, 9H); LCMS (Method G): Rt = 1.66 min, m/z = 562.3 $[M+H]^+$; HPLC (Method D): Rt = 2.20 min, 96.12%; Chiral SFC (Method AG): Rt = 3.72 min, 98.63%.

Example 73. (*E1*)-5-Fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 320)

Example 74. (*E2*)-5-Fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 321)



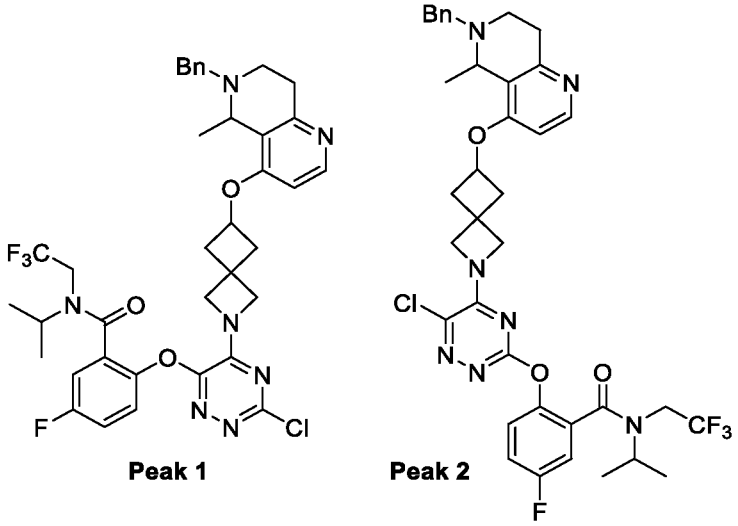
Step 1. (±)-6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine



To a stirred solution of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (9.2 g, 23.84 mmol) in DCM (200 mL), TEA (10.05 mL, 71.5 mmol) and 3,5,6-trichloro-1,2,4-triazine (4.40 g, 23.84 mmol) were added at 0 °C. The reaction was stirred at RT for 20 min. The reaction progress was monitored by

TLC (10% MeOH in DCM). The reaction was quenched with ice water (100 mL) and extracted with DCM (2 x 250 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to afford (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (11.3 g, 83% yield) as a solid. LCMS (Method G): Rt = 2.22 min, m/z = 497.2 $[M+H]^+$; 86.94%.

Step 2. (±)-2-((5-(6-((6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide and (±)-2-((5-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3] heptan-6-yl)oxy)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 2 equivalents of 5-fluoro-2-hydroxy-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl) benzamide, except that 3 equivalents of DBU was used. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM), then by achiral SFC purification (Method I) to obtain both regioisomers.

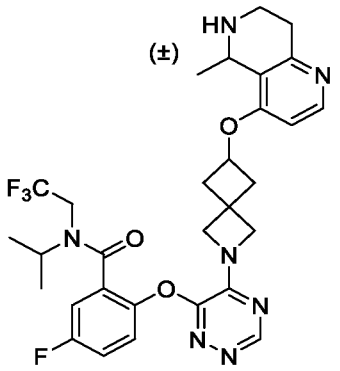
Peak 1. (±)-2-((5-(6-((6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 16.23%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (t, J = 5.5 Hz, 1H), 7.54 - 7.39 (m, 3H), 7.37 - 7.18 (m, 5H), 6.69 (t, J = 6.5 Hz, 1H), 4.83 - 4.71 (m, 1H), 4.67 - 4.50 (m, 2H), 4.31 - 3.93 (m, 5H), 3.81 - 3.71 (m, 2H), 3.65 - 3.55 (m, 1H), 3.12 - 2.99 (m, 1H), 2.93 - 2.70 (m, 4H), 2.65 - 2.56 (m, 1H), 2.32 - 2.17 (m, 2H), 1.34 - 1.20 (m, 3H), 1.16 - 0.71 (m, 6H); LCMS (Method B): Rt = 1.62 min, m/z = 740.3 $[M+H]^+$; 96.63%.

Peak 2. (±)-2-((5-(6-((6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 13.15%; LCMS (Method B): Rt = 1.66 min, m/z = 740.3 $[M+H]^+$; 97.81%.

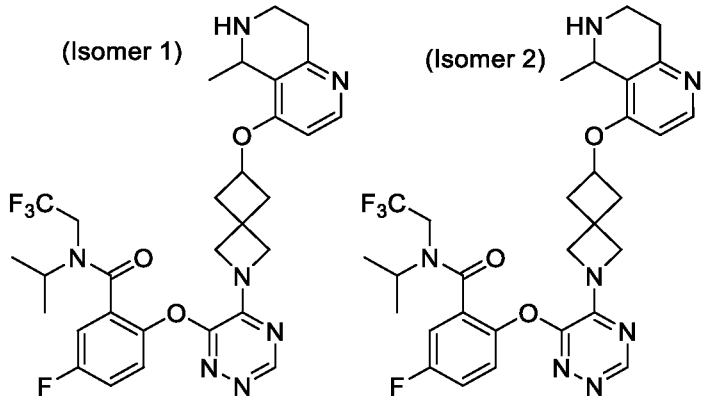
Step 3. (±)-5-Fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



To a stirred solution of (±)-2-((5-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (750 mg, 1.013 mmol) in 2,2,2-trifluoroethanol (20 mL), Pd/C (539 mg, 0.507 mmol) was added. The reaction was stirred at RT for 8 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (3 x 25 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (600 mg, 85% yield). LCMS (Method G): Rt = 1.66 min, m/z = 616.4 $[M+H]^+$; HPLC (Method D): Rt = 4.79 min, 88.05%. This material was used without further purification.

Step 4. (E1)-5-Fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide and (E2)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-

tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide

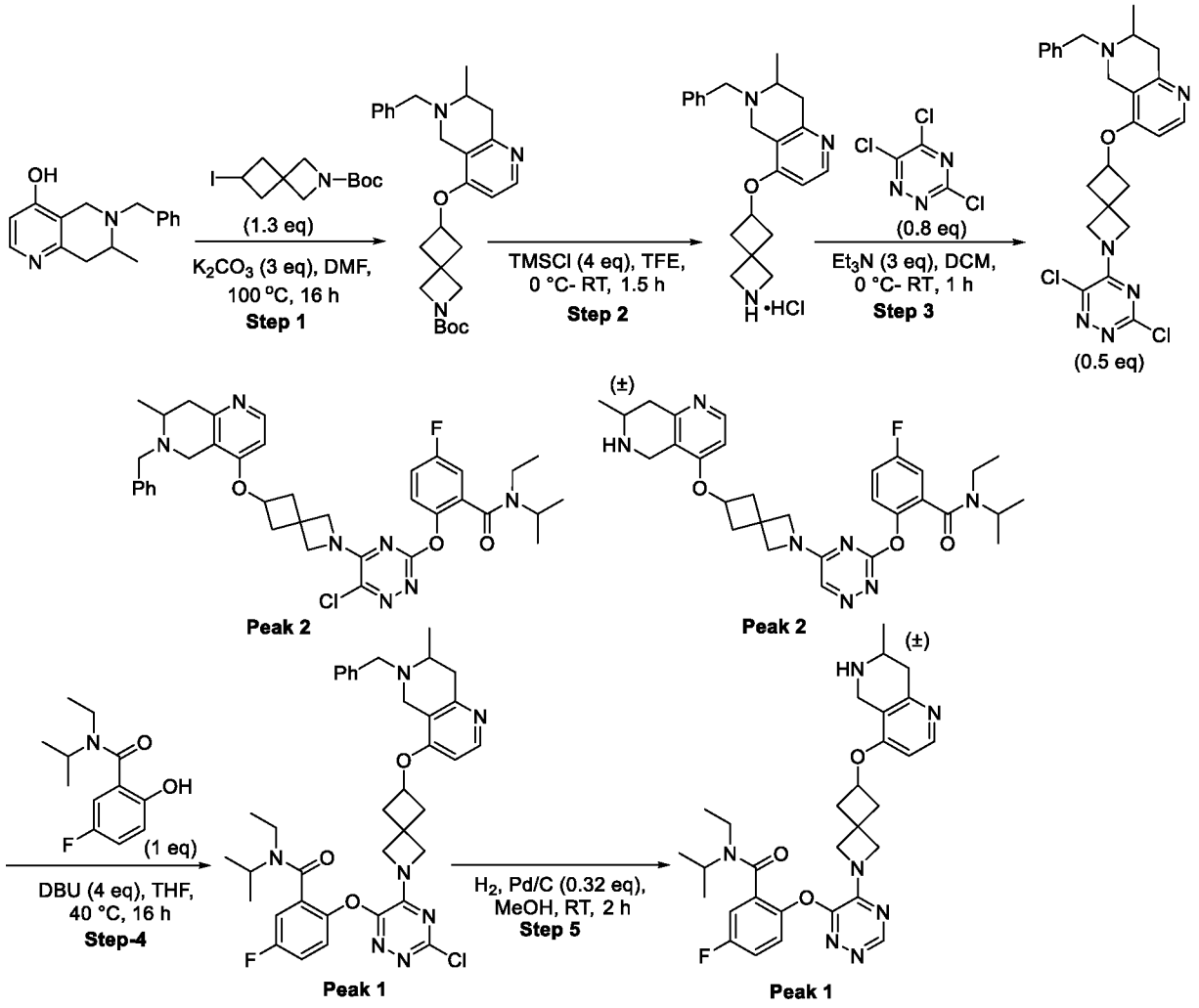


(±)-5-Fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (600 mg, 0.975 mmol) was purified by chiral Prep SFC (Method K). ^{1}H NMR showed impurities in both separated compounds. Therefore, Isomer 1 and Isomer 2 were re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (*E1*)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (148.44 mg, 24.31% yield) and (*E2*)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (147.88 mg, 24.44% yield) as solids.

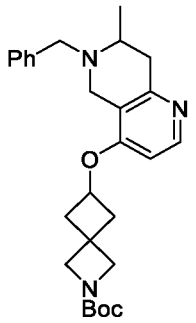
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.52 - 7.39 (m, 3H), 6.66 (br d, J = 4.6 Hz, 1H), 4.77 (quin, J = 6.6 Hz, 1H), 4.64 - 4.44 (m, 2H), 4.33 - 4.00 (m, 5H), 3.83 - 3.74 (m, 1H), 3.12 - 3.02 (m, 1H), 2.93 - 2.76 (m, 3H), 2.74 - 2.58 (m, 2H), 2.32 - 2.18 (m, 1H), 1.34 - 1.20 (m, 3H), 1.14 - 0.66 (m, 6H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.64 min, m/z = 616.5 $[M+H]^+$; HPLC (Method A): Rt = 5.20 min, 98.28%; Chiral SFC (Method AH): Rt = 4.45 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.52 - 7.39 (m, 3H), 6.66 (br d, J = 5.1 Hz, 1H), 4.82 - 4.74 (m, 1H), 4.66 - 4.45 (m, 2H), 4.33 - 4.00 (m, 5H), 3.85 - 3.72 (m, 1H), 3.13 - 3.04 (m, 1H), 2.93 - 2.78 (m, 3H), 2.74 - 2.60 (m, 2H), 2.32 - 2.13 (m, 1H), 1.34 - 1.10 (m, 3H), 1.14 - 0.64 (m, 6H), two protons merged with solvent peaks; LCMS (Method D): Rt = 1.61 min, m/z = 616.3 $[M+H]^+$; HPLC (Method A): Rt = 4.83 min, 99.18%; Chiral SFC (Method AH): Rt = 6.28 min, 98.78%.

Example 75. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 258)



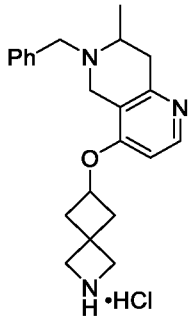
Step 1. (±)-tert-Butyl 6-((6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (500 mg, 1.966 mmol) in DMF (5 mL), powdered K_2CO_3 (815 mg, 5.90 mmol) was added at RT under a nitrogen atmosphere. *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (826

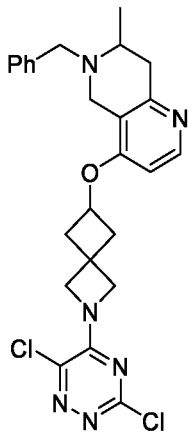
mg, 2.56 mmol) was added to this reaction mixture and stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to 0 °C, quenched with ice-cold water (50 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 13-15% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (400 mg, 39.4% yield) as a solid. LCMS (Method G): Rt = 2.30 min, m/z = 450.4 $[M+H]^+$, 87.16%.

Step 2. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine



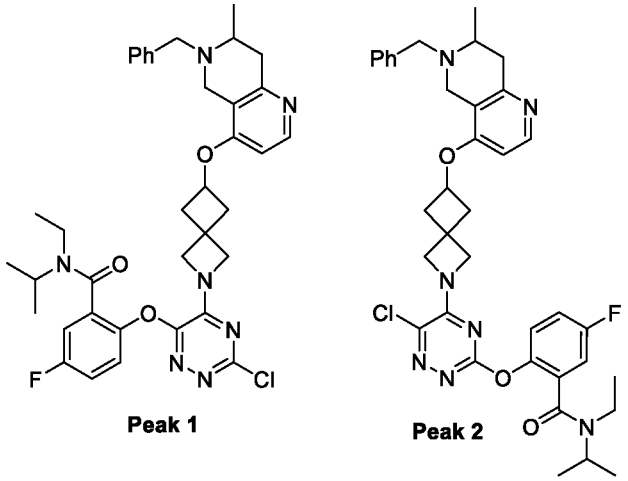
To a stirred solution (±)-*tert*-butyl 6-((6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (400 mg, 0.890 mmol) in 2,2,2-trifluoroethanol (5 mL), TMSCl (0.455 mL, 3.56 mmol) was slowly added at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude (±) 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (350 mg, 92% yield) as a solid. LCMS (Method I): Rt = 1.91 min, m/z = 350.2 $[M+H]^+$, 90.22%. This material was used without further purification.

Step 3. (±)-*6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine*



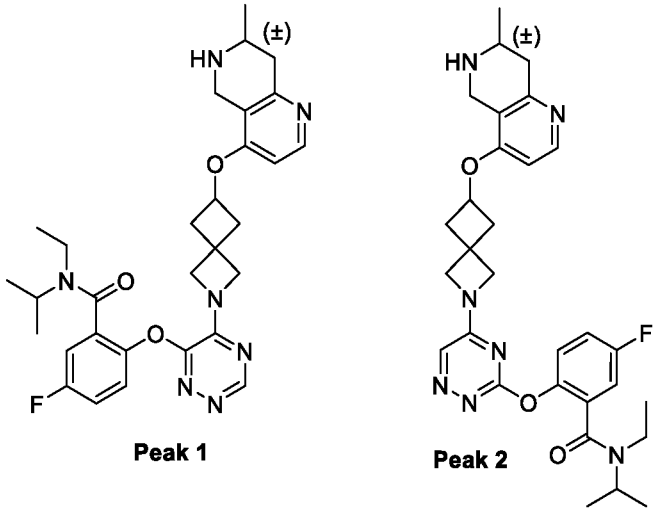
In a 100 mL round bottom flask under a nitrogen atmosphere, (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (350 mg, 0.816 mmol) was added in DCM (10 mL). Et_3N (0.341 mL, 2.449 mmol) was added to this solution at 0 °C, and 3,5,6-trichloro-1,2,4-triazine (120 mg, 0.653 mmol) was added. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (180 mg, 40.4% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (d, J = 5.5 Hz, 1H), 7.38 - 7.31 (m, 5H), 6.67 (d, J = 5.5 Hz, 1H), 4.80 - 4.65 (m, 3H), 4.27 - 4.07 (m, 2H), 3.55 - 3.41 (m, 2H), 3.19 - 3.09 (m, 2H), 3.05 - 2.95 (m, 1H), 2.85 - 2.74 (m, 2H), 2.23 - 2.13 (m, 2H), 1.96 - 1.85 (m, 2H), 1.05 (br d, J = 6.4 Hz, 3H); LCMS (Method G): Rt = 2.15 min, m/z = 497.4 $[M+H]^+$, 91.13%.

Step 4. (±)-(2-((5-(6-((6-Benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



To a stirred solution of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (1.0 g, 4.44 mmol) in THF (10 mL), DBU (2.68 mL, 17.76 mmol) was added at 0 °C. To this reaction mixture, (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (1.104 g, 2.220 mmol) was added. The reaction was stirred at 40 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to RT, quenched with water (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using methanol in DCM (product was eluted at 10% MeOH in DCM) to obtain a mixture of regioisomers, (±)-2-((5-(6-((6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (1.1 g, 34.0% yield) as a semi-solid. LCMS (Method G): Rt = 2.31 min, m/z = 686.6 $[M+H]^+$, 96.57%. The mixture of regioisomers was used without further purification.

Step 5. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



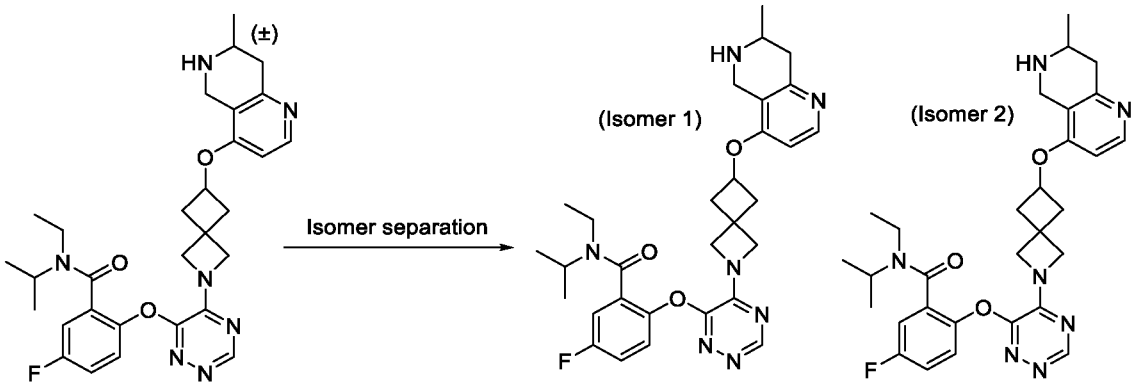
In a 100 mL round bottom flask under an argon atmosphere, a mixture of 2-((5-(6-((6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (0.150 g, 0.219 mmol) was added in MeOH (10 mL). To this solution, dry Pd-C (75 mg, 0.322 mmol) was added, and the reaction was stirred at RT for 2 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude was purified by achiral Prep SFC (method K) to obtain both regioisomers.

Peak 1. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (19.18 mg, 15.28% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.67 (d, J = 5.6 Hz, 1H), 4.81 - 4.73 (m, 1H), 4.66 - 4.49 (m, 2H), 4.26 - 4.10 (m, 2H), 3.93 - 3.84 (m, 1H), 3.70 - 3.58 (m, 2H), 3.16 - 2.98 (m, 2H), 2.93 - 2.78 (m, 3H), 2.71 - 2.66 (m, 1H), 2.44 - 2.38 (m, 1H), 2.36 - 2.27 (m, 3H), 1.14 - 0.66 (m, 12H); LCMS (Method G): Rt = 1.72 min, m/z = 562.4 $[M+H]^+$; HPLC (Method A): Rt = 4.54 min, 97.81%; Chiral SFC (Method AT): Peak 1: Rt = 3.00 min, 47.60, Peak 2: 3.22 min, 51.66%.

Peak 2. (±)-2-((5-(6-((6-Benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (12 mg, 8.14% yield) as a solid. LCMS (Method G): Rt = 1.74 min, m/z = 562.4 $[M+H]^+$, 87.82%.

Example 76. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 286)

Example 77. *(E2)*-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 287)

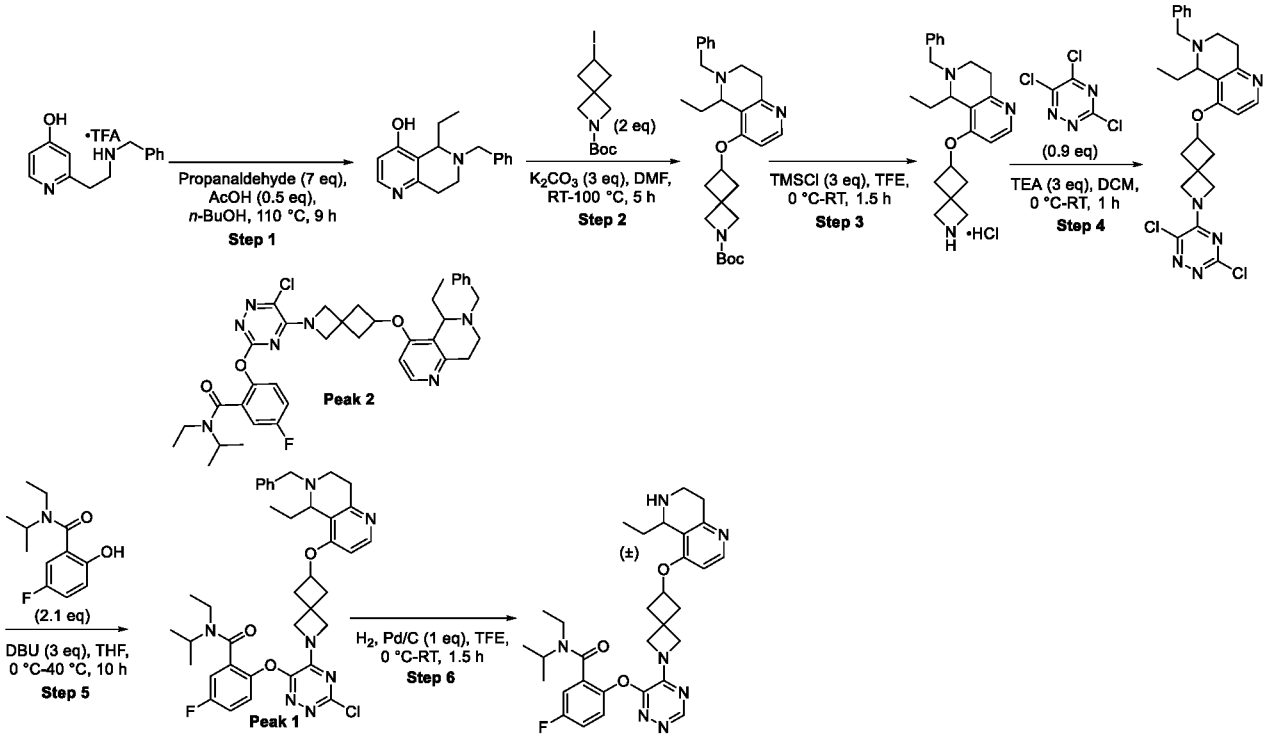


(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (260 mg) was purified by chiral Prep SFC (Method K) to obtain both isomers. (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (43.27 mg, 16.41% yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (22.75 mg, 8.63% yield) as solids.

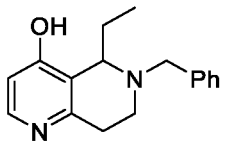
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.66 (d, J = 5.5 Hz, 1H), 4.80-4.74 (m, 1H), 4.67 - 4.49 (m, 2H), 4.33 - 4.11 (m, 2H), 3.92 - 3.84 (m, 1H), 3.65-3.61 (m, 2H), 3.46 - 3.39 (m, 1H), 3.16 - 2.99 (m, 2H), 2.91 - 2.77 (m, 4H), 2.40 - 2.29 (m, 3H), 1.15 - 0.95 (m, 12H); LCMS (Method G): Rt = 1.63 min, m/z = 562.4 $[M+H]^+$; HPLC (Method A): Rt = 4.52 min, 98.87%; Chiral SFC (Method K): Rt = 4.48 min, 98.93%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.67 (d, J = 5.6 Hz, 1H), 4.81 - 4.73 (m, 1H), 4.65 - 4.50 (m, 2H), 4.32 - 4.14 (m, 2H), 3.93 - 3.83 (m, 1H), 3.67-3.61 (m, 2H), 3.46 - 3.39 (m, 1H), 3.15 - 2.99 (m, 2H), 2.92 - 2.78 (m, 4H), 2.36 - 2.29 (m, 3H), 1.16 - 0.67 (m, 12H); LCMS (Method G): Rt = 1.67 min, m/z = 562.3 $[M+H]^+$; HPLC (Method A): Rt = 4.53 min, 97.94%; Chiral SFC (Method K): Rt = 4.91 min, 100%.

Example.78. (±)-*N*-Ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 219)

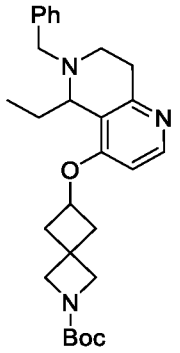


Step 1. (±)-6-Benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



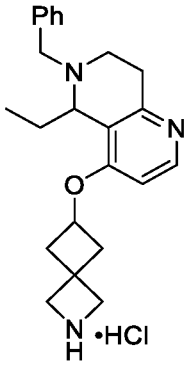
In a 200 mL stainless steel mini clave, 2-(2-(benzylamino)ethyl)pyridin-4-ol (7.5 g, 32.9 mmol) was added in *n*-butanol (45 mL), and the solution was degassed with argon gas for 10 min. AcOH (0.939 mL, 16.43 mmol) and propionaldehyde (16.49 mL, 230 mmol) were added to this solution. The reaction was stirred at 110 °C for 9 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to afford (±)-6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.3 g, 4.41 mmol, 13.42% yield) as a semi-solid. LCMS (Method G): Rt = 1.54 min, m/z = 269.1 $[M+H]^+$, 91.45%.

Step 2. (±)-tert-Butyl 6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.2 g, 4.47 mmol) in DMF (10 mL), powdered K_2CO_3 (1.854 g, 13.41 mmol) and *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (2.89 g, 8.94 mmol) were added at RT. The reaction was stirred at 100 °C for 5 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with cold water (50 mL) and brine solution (50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (920 mg, 39.1% yield). LCMS (Method B): Rt = 1.60 min, m/z = 464.4 $[M+H]^+$, 88.69%.

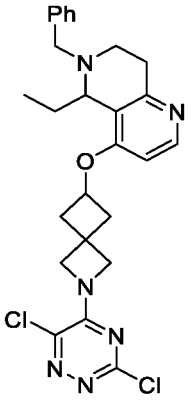
Step 3. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



In a 50 mL round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.9 g, 1.941 mmol) was added in TFE (10 mL). TMSCl (0.744 mL, 5.82 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-

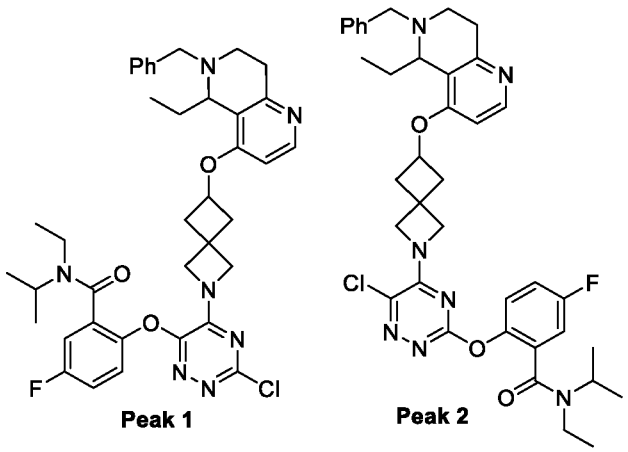
6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (760 mg, 98% yield) as a solid. LCMS (Method B): Rt = 0.67 min, m/z = 364.2 $[M+H]^+$, 67.81%. This material was used without further purification.

Step 4. (±)-6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine



To a stirred solution of (±)-3,5,6-trichloro-1,2,4-triazine (0.325 g, 1.762 mmol) in DCM (2 mL), TEA (0.737 mL, 5.29 mmol) and 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (0.634 g, 1.586 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 4% MeOH in DCM) to obtain (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (0.660 g, 62.2% yield) as a solid. LCMS (Method G): Rt = 2.23 min, m/z = 511.4 $[M+H]^+$, 85.00%.

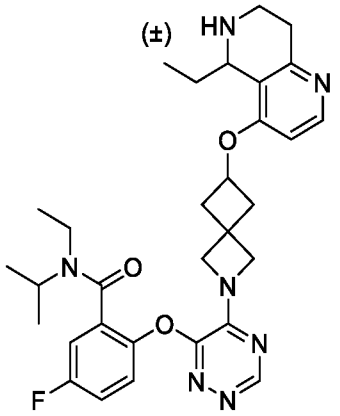
Step 5. (±)-2-((5-(6-((6-Benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a stirred solution of (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (600 mg, 1.173 mmol) in THF (15 mL), *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (555 mg, 2.464 mmol) and DBU (0.530 mL, 3.52 mmol) were added at 0 °C. The reaction was stirred at 40 °C for 10 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with water (100 mL) and brine solution (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 66%) to afford (±)-2-((5-(6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (235 mg, 24.93% yield, peak 1) as a viscous liquid. LCMS (Method B): Rt = 1.69 min, m/z = 700.3 $[M+H]^+$, 87.16%.

Note: Peak 2 was not isolated.

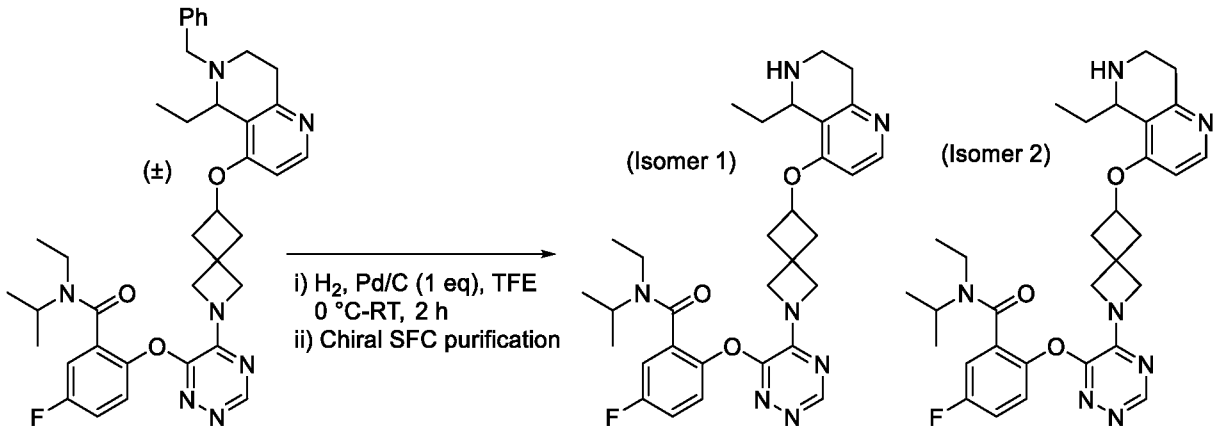
Step 6. (±)-N-Ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropylbenzamide



In a 25 mL round bottom flask under a nitrogen atmosphere, (±)-2-((5-(6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (50 mg, 0.071 mmol) was added in TFE (3 mL). Pd-C (76 mg, 0.071 mmol) was added to this solution, and the reaction was stirred at RT for 1.5 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (15 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*N*-ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (19 mg, 0.032 mmol, 45.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.41 - 7.28 (m, 2H), 6.66 (d, J = 5.5 Hz, 1H), 4.77 (quin, J = 6.4 Hz, 1H), 4.70 - 4.45 (m, 2H), 4.36 - 4.07 (m, 2H), 3.80 - 3.71 (m, 1H), 3.70 - 3.55 (m, 1H), 3.50 - 3.42 (m, 1H), 3.19 - 2.95 (m, 2H), 2.94 - 2.76 (m, 3H), 2.70 - 2.59 (m, 3H), 2.32 - 2.20 (m, 2H), 1.70 - 1.44 (m, 2H), 1.20 - 0.59 (m, 12H); LCMS (Method D): Rt = 1.67 min, m/z = 576.4 $[M+H]^+$; HPLC (Method A): Rt = 4.78 min, 98.01%; Chiral SFC (Method J): Peak 1: Rt = 3.50 min, 50.02%, Peak 2: Rt = 4.27 min, 49.98%.

Example.79. (*E1*)-*N*-Ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 230)

Example.80. (*E2*)-*N*-Ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 231)



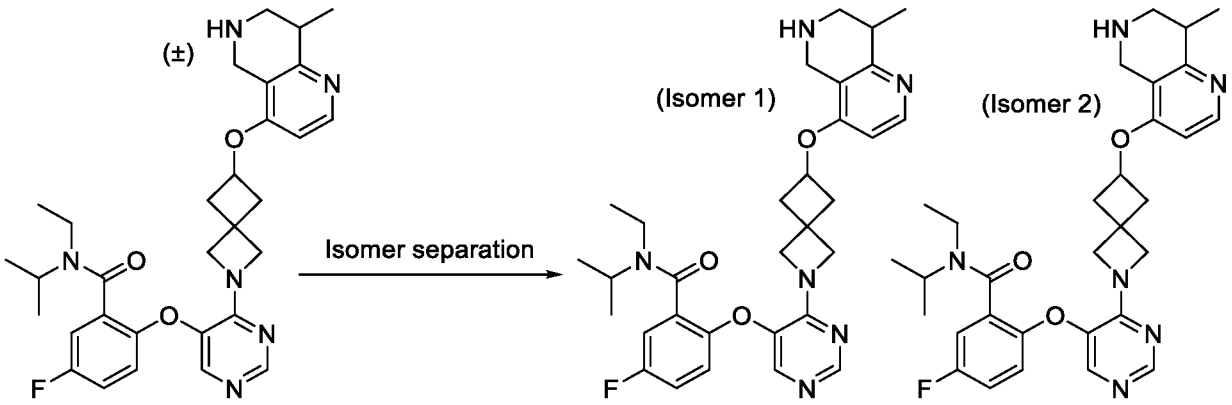
Both isomers were synthesized following the procedure described for the synthesis of Example 78, step 6, starting with (±)-2-((5-(6-((6-benzyl-5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (180 mg, 0.257 mmol). The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH), then by chiral Prep SFC (Method E) to obtain both isomers, (*E1*)-*N*-ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (25 mg, 16.84% yield) and (*E2*)-*N*-ethyl-2-((5-(6-((5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (29 mg, 19.55% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 6.66 (d, J = 5.6 Hz, 1H), 4.82 - 4.73 (m, 1H), 4.68 - 4.51 (m, 2H), 4.35 - 4.09 (m, 2H), 3.80 - 3.71 (m, 1H), 3.69 - 3.56 (m, 1H), 3.46 - 3.37 (m, 1H), 3.19 - 2.96 (m, 2H), 2.94 - 2.77 (m, 3H), 2.70 - 2.57 (m, 3H), 2.32 - 2.23 (m, 2H), 1.69 - 1.46 (m, 2H), 1.20 - 0.61 (m, 12H); LCMS (Method G): Rt = 1.68 min, m/z = 576.5 $[M+H]^+$; HPLC (Method A): Rt = 4.61 min, 99.70%; Chiral SFC (Method J): Rt = 3.47 min, 99.70%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.40 - 7.30 (m, 2H), 6.66 (d, J = 5.6 Hz, 1H), 4.83 - 4.72 (m, 1H), 4.69 - 4.48 (m, 2H), 4.33 - 4.12 (m, 2H), 3.75 (br d, J = 7.9 Hz, 1H), 3.69 - 3.57 (m, 1H), 3.47 - 3.39 (m, 1H), 3.18 - 2.95 (m, 2H), 2.94 - 2.76 (m, 3H), 2.74 - 2.58 (m, 3H), 2.33 - 2.19 (m, 2H), 1.71 - 1.42 (m, 2H), 1.19 - 0.61 (m, 12H); LCMS (Method G): Rt = 1.67 min, m/z = 576.5 $[M+H]^+$; HPLC (Method A): Rt = 4.61 min, 99.78%; Chiral SFC (Method J): Rt = 4.30 min, 95.38%.

Example 81. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 203)

Example 82. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 204)



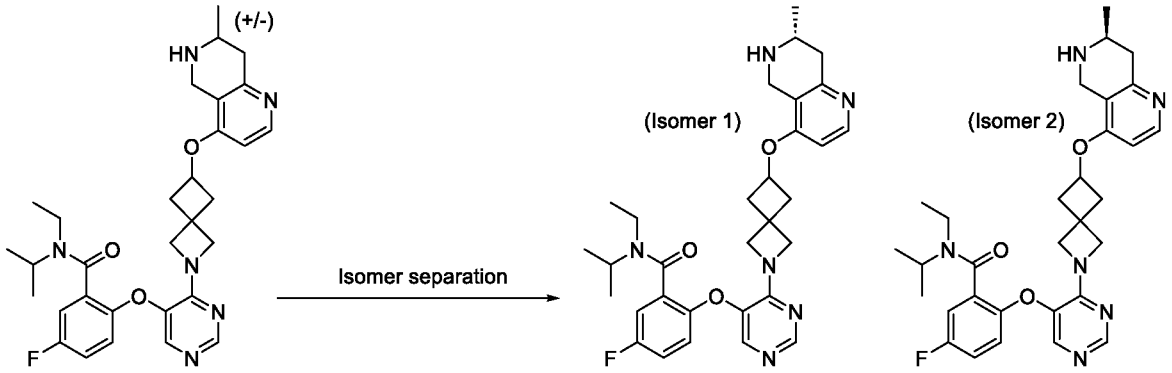
(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (450 mg) was purified by chiral Prep SFC (Method J) obtain (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (94.24 mg, 20.91% yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (92.44 mg, 20% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.67 (s, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.66 - 6.60 (m, 1H), 4.76 - 4.66 (m, 1H), 4.47 - 4.08 (m, 4H), 3.81 - 3.73 (m, 1H), 3.71 (s, 2H), 3.46 - 3.37 (m, 1H), 3.27 - 3.12 (m, 1H), 3.05 (dd, J = 4.7, 12.4 Hz, 1H), 2.83 - 2.70 (m, 4H), 2.68 - 2.61 (m, 1H), 2.29 - 2.18 (m, 2H), 1.22 (d, J = 7.0 Hz, 3H), 1.18 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.06 min, m/z = 561.3 $[M+H]^+$; 97.36%; HPLC (Method D): Rt = 2.01 min, 97.71%; Chiral SFC (Method AF): Rt = 7.14 min, 97.65%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.66 - 6.61 (m, 1H), 4.78 - 4.67 (m, 1H), 4.47 - 4.07 (m, 4H), 3.80 - 3.73 (m, 1H), 3.71 (s, 2H), 3.44 - 3.37 (m, 1H), 3.27 - 3.12 (m, 1H), 3.05 (dd, J = 4.8, 12.3 Hz, 1H), 2.83 - 2.71 (m, 4H), 2.66 - 2.61 (m, 1H), 2.29 - 2.17 (m, 2H), 1.22 (d, J = 7.0 Hz, 3H), 1.14 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.69 min, m/z = 561.3 $[M+H]^+$; 99.85%; HPLC (Method A): Rt = 4.78 min, 98.46%; Chiral SFC (Method AF): Rt = 8.15 min, 97.56%.

Example 83. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 193)

Example 84. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 194)



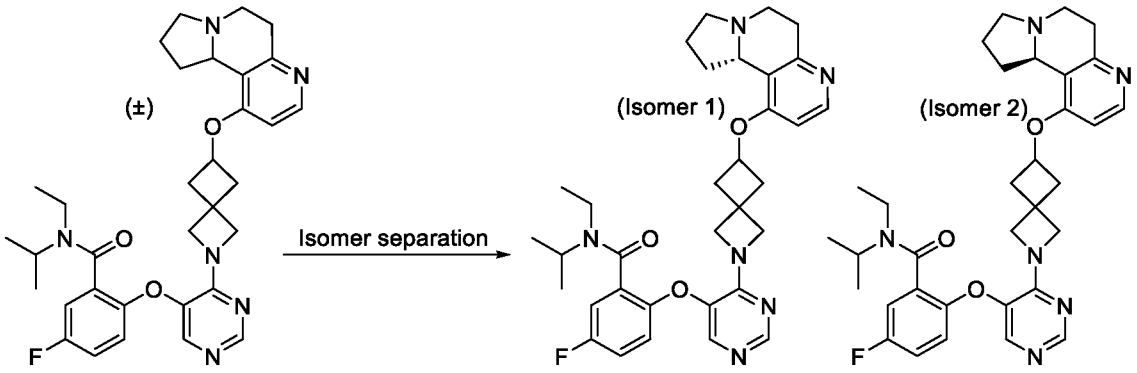
(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (668 mg) was purified by chiral Prep SFC (Method O) to obtain (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (149.31 mg, 22.3 % yield) and (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.104 g, 15.43% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): 8.31 - 8.26 (m, 1H), 8.18 - 8.15 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.67 - 6.63 (m, 1H), 4.80 - 4.67 (m, 1H), 4.46 - 4.06 (m, 4H), 3.88 (d, J = 16.8 Hz, 1H), 3.80 - 3.72 (m, 1H), 3.64 (d, J = 16.8 Hz, 1H), 3.45 - 3.38 (m, 1H), 3.27 - 3.13 (m, 1H), 2.92 - 2.83 (m, 1H), 2.81 - 2.71 (m, 2H), 2.70 - 2.67 (m, 1H), 2.43 - 2.35 (m, 2H), 2.30 - 2.19 (m, 2H), 1.22 - 0.97 (m, 12H); LCMS (Method D): Rt = 1.68 min, m/z = 561.3 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 99.80%, Chiral SFC (Method AW): Rt = 3.49 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 - 8.15 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.67 - 6.63 (m, 1H), 4.77 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.89 (d, J = 16.8 Hz, 1H), 3.80 - 3.72 (m, 1H), 3.65 (d, J = 16.6 Hz, 1H), 3.44 - 3.37 (m, 1H), 3.27 - 3.11 (m, 1H), 2.94 - 2.85 (m, 1H), 2.82 - 2.72 (m, 2H), 2.71 - 2.66 (m, 1H), 2.44 - 2.35 (m, 2H), 2.30 - 2.19 (m, 2H), 1.22 - 0.97 (m, 12H); LCMS (Method D): Rt = 1.68 min, m/z = 561.3 $[M+H]^+$; HPLC (Method A): Rt = 4.73 min, 99.08%, Chiral SFC (Method AW): Rt = 3.95 min, 100%.

Example 85. (*E1*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 249)

Example 86. (*E2*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 250)



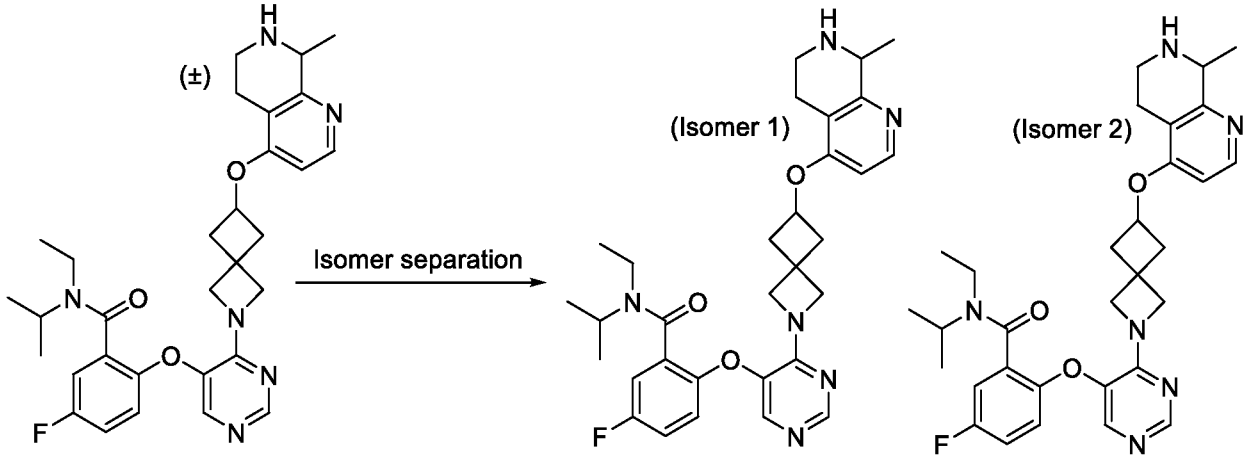
(±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (110 mg, 0.187 mmol) was purified by chiral Prep SFC (Method L) to obtain (*E1*)-*N*-ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (43 mg, 38.7% yield) and (*E2*)-*N*-ethyl-5-fluoro-2-((4-(6-((5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (42 mg, 37.8% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 - 7.64 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.67 ((d, J = 5.6 Hz, 1H), 4.80 - 4.65 (m, 1H), 4.46 - 4.07 (m, 4H), 3.81 - 3.70 (m, 1H), 3.65 (br t, J = 8.1 Hz, 1H), 3.43 - 3.38 (m, 1H), 3.27 - 3.13 (m, 1H), 3.01 - 2.83 (m, 4H), 2.82 - 2.73 (m, 2H), 2.72 - 2.60 (m, 2H), 2.43 - 2.36 (m, 1H), 2.30 - 2.19 (m, 2H), 1.85 - 1.66 (m, 2H), 1.53 - 1.42 (m, 1H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.84 min, m/z = 587.4 $[M+H]^+$; HPLC (Method A): Rt = 5.19 min, 97.84%; Chiral SFC (Method Z): Rt = 2.93 min, 99.82%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.08 (m, 4H), 3.79 - 3.70 (m, 1H), 3.71 - 3.57 (m, 1H), 3.4 - 3.37 (m, 1H), 3.22 - 3.11 (m, 1H), 3.00 - 2.84 (m, 4H), 2.82 - 2.73 (m, 2H), 2.71 - 2.63 (m, 2H), 2.42 - 2.37 (m, 1H), 2.30 - 2.18 (m, 2H), 1.86 - 1.66 (m, 2H), 1.52 - 1.39 (m, 1H), 1.23 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.89 min, m/z = 587.4 $[M+H]^+$; HPLC (Method A): Rt = 5.21 min, 98.73%; Chiral SFC (Method Z): Rt = 4.14 min, 100%.

Example 87. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 224)

Example 88. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 225)

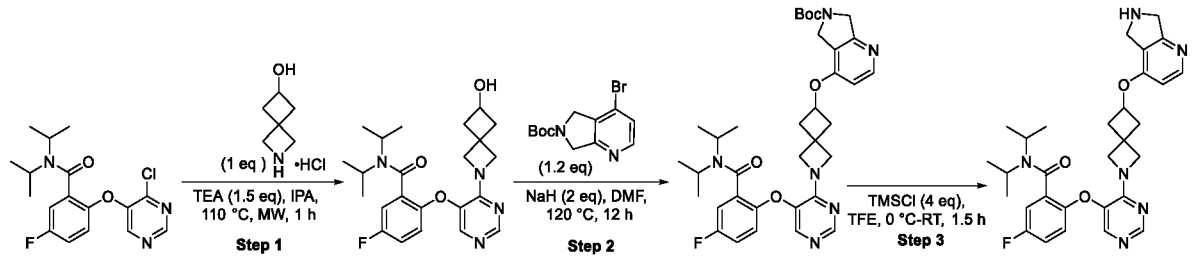


(±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (95 mg) was purified by chiral Prep SFC (Method J) to obtain both isomers (isomer 1: 30 mg and isomer 2: 50 mg). Due to presence of impurity in separated isomers, isomer 1 and 2 were re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) separately, to obtain (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (10.45 mg, 10.65 % yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (11.23 mg, 11.61 % yield) as solids.

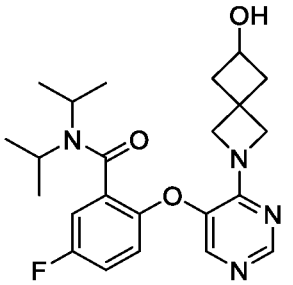
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.67 - 6.63 (m, 1H), 4.78 - 4.69 (m, 1H), 4.42 - 4.08 (m, 4H), 3.89 - 3.81 (m, 1H), 3.81 - 3.70 (m, 1H), 3.44 - 3.38 (m, 2H), 3.25 - 3.14 (m, 2H), 3.12 - 3.04 (m, 1H), 2.83 - 2.74 (m, 3H), 2.30 - 2.19 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.75 min, m/z = 561.4 $[M+H]^+$; HPLC (Method A): Rt = 4.69 min, 98.20%; Chiral SFC (Method AF): Rt = 8.81 min, 98.43%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.66 - 6.62 (m, 1H), 4.76 - 4.67 (m, 1H), 4.45 - 4.08 (m, 4H), 3.88 - 3.80 (m, 1H), 3.79 - 3.69 (m, 1H), 3.44 - 3.38 (m, 2H), 3.25 - 3.13 (m, 2H), 3.10 - 3.03 (m, 1H), 2.84 - 2.73 (m, 3H), 2.28 - 2.18 (m, 2H), 1.35 (d, J = 6.8 Hz, 3H), 1.22 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.69 min, m/z = 561.4 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 99.50%; Chiral SFC (Method AF): Rt = 9.51 min, 94.06%.

Example 89. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (Compound No. 16)

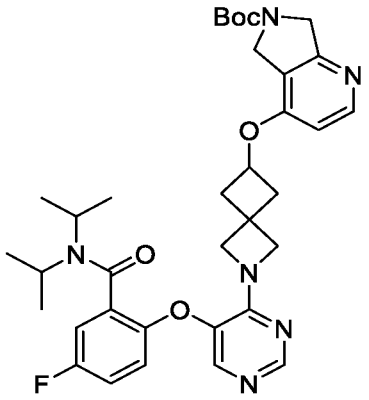


Step 1. 5-Fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N,N-diisopropylbenzamide



In a 10 mL microwave vial, 2-azaspiro[3.3]heptan-6-ol hydrochloride (255 mg, 1.705 mmol) was dissolved in IPA (3 mL) and TEA (431 mg, 4.26 mmol) and 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (300 mg, 0.853 mmol) were added at RT. The vial was sealed under a nitrogen atmosphere, and the reaction was stirred at 110 °C for 1 h in a microwave oven. The progress of the reaction was monitored by LCMS (Method D). After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 55-65% EtOAc in hexane) to obtain 5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*,*N*-diisopropylbenzamide (290 mg, 66.0% yield) as a solid. LCMS (Method D): Rt = 1.60 min, m/z = 429.2 $[M+H]^+$, 83.20%.

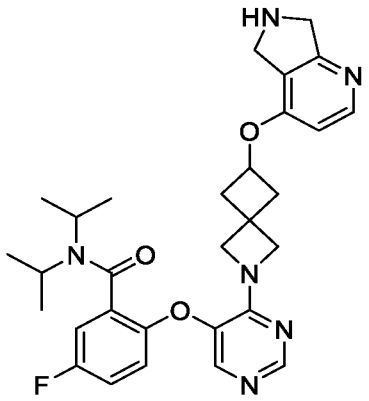
Step 2. tert-Butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 21, step 1, starting with *tert*-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 1 equivalent of 5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*,*N*-diisopropylbenzamide was used. The reaction was stirred at 120 °C. After completion, the reaction was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a semi-solid.

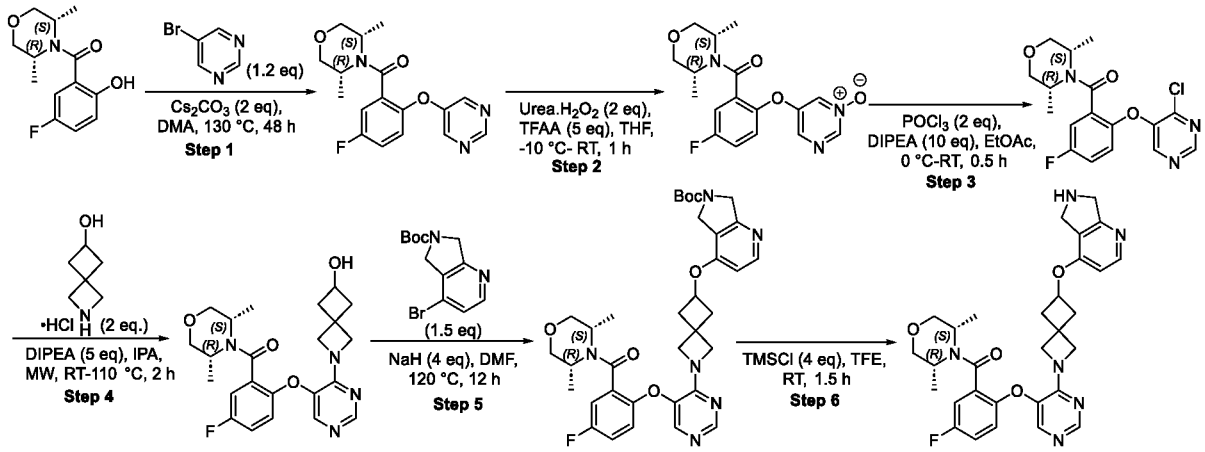
Yield: 24.81%; LCMS (Method D): Rt = 2.14 min, m/z = 647.1 $[M+H]^+$, 32.17%. This material was used without further purification.

Step 3. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide

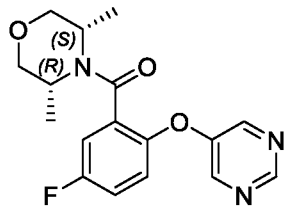


This compound was synthesized following the procedure described for the synthesis of Example 21, step 2, starting with *tert*-butyl 4-((2-(5-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to obtain crude 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide hydrochloride. The crude was purified by Prep HPLC (Method AL) to obtain 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide as a solid. Yield: 19.78%; NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.21 (d, J = 5.7 Hz, 1H), 7.74 (s, 1H), 7.28 - 7.17 (m, 2H), 7.08 - 7.01 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 (q, J = 6.7 Hz, 1H), 4.45 (s, 1H), 4.34 - 4.07 (m, 4H), 4.03 (br s, 2H), 3.99 (br s, 2H), 3.73 - 3.62 (m, 1H), 3.58 - 3.45 (m, 1H), 2.84 - 2.74 (m, 2H), 2.30 - 2.21 (m, 2H), 1.44 (d, J = 6.7 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H); LCMS (Method D): Rt = 1.64 min, m/z = 547.2 $[M+H]^+$; HPLC (Method A): Rt = 4.85 min, 97.82%.

Example 90. (2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((*3S,5R*)-3,5-dimethylmorpholino)methanone (Compound No. 21)



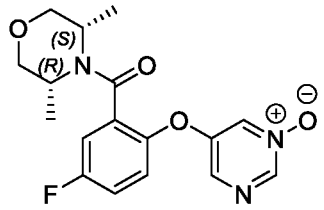
Step 1. ((3R,5S)-3,5-Dimethylmorpholino)(5-fluoro-2-(pyrimidin-5-yloxy)phenyl)methanone



To a stirred solution of ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone (5.2 g, 20.53 mmol) in DMA (50 mL), Cs_2CO_3 (13.38 g, 41.1

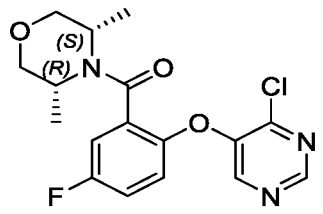
mmol) was added at RT under a nitrogen atmosphere. 5-Bromopyrimidine (3.92 g, 24.64 mmol) was added and the reaction was stirred at 130 °C for 48 h. The progress of the reaction was monitored by TLC (60% EtOAc in hexane). After completion, the reaction was cooled to RT, quenched with cold water (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 50% EtOAc in hexane) to afford ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-(pyrimidin-5-yloxy)phenyl)methanone (4.1 g, 41.0% yield) as a solid. LCMS (Method D): Rt = 1.43 min, m/z =332.1 $[M+H]^+$, 68.15%.

Step 2. 5-(2-((3R,5S)-3,5-Dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidine 1-oxide



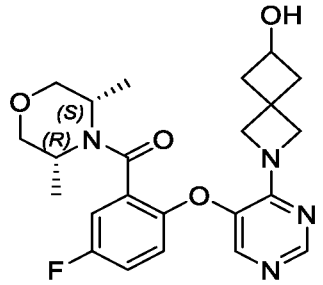
In a 250 mL two-neck round bottom flask under a nitrogen atmosphere, ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-(pyrimidin-5-yloxy)phenyl)methanone (4.0 g, 12.07 mmol) was dissolved in THF (40 mL) at RT. To this reaction mixture, urea hydrogen peroxide (2.271 g, 24.14 mmol) and TFAA (8.17 mL, 60.4 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with saturated sodium bicarbonate (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with 1M $Na_2S_2O_3$ solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 5-(2-((3*R*,5*S*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidine 1-oxide (4.0 g, 42.1% yield)) as a semi-solid. LCMS (Method D): Rt = 1.27 min, m/z = 348.0 $[M+H]^+$, 44.20%. This material was used without further purification.

Step 3. (2-((4-Chloropyrimidin-5-yl)oxy)-5-fluorophenyl)((3R,5S)-3,5-dimethylmorpholino)methanone



In a 250 mL two-neck round bottom flask under a nitrogen atmosphere, 5-(2-((3*R*,5*S*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidine 1-oxide (4.0 g, 11.52 mmol) was dissolved in EtOAc (40 mL) at RT. The reaction was cooled to -15 °C, DIPEA (20.11 mL, 115 mmol) and $POCl_3$ (2.249 mL, 23.03 mmol) were added, and the reaction was stirred at 0 °C for 30 min. The reaction was slowly warmed to RT and stirred for 0.5 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with saturated sodium bicarbonate (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 35% EtOAc in hexane) to afford (2-((4-chloropyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone (650 mg, 12.93% yield) as a semi-solid. LCMS (Method D): Rt = 1.63 min, m/z = 366.0 $[M+H]^+$, 83.81%.

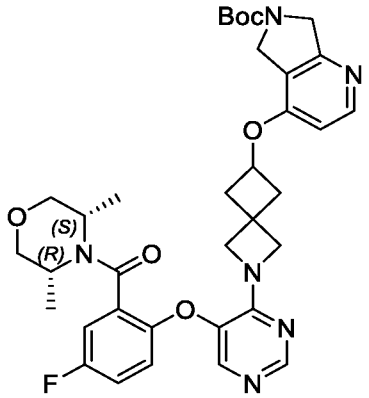
Step 4. ((3S,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone



To a solution of 2-azaspiro[3.3]heptan-6-ol hydrochloride (491 mg, 3.28 mmol) in IPA (5 mL), DIPEA (4.87 mL, 27.3 mmol) was added at RT. To this reaction mixture,(2-((4-chloropyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone (600 mg, 1.640 mmol) was added. The reaction was stirred at 110 °C for 2 h in a microwave oven. The progress of the reaction was monitored by TLC (100% EtOAc in hexane). After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH and DCM (product was eluted at 5% MeOH in DCM) to obtain ((3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone

(400 mg, 44.0% yield) as a semi-solid. LCMS (Method D): Rt = 1.38 min, m/z = 443.1 $[M+H]^+$, 79.89%.

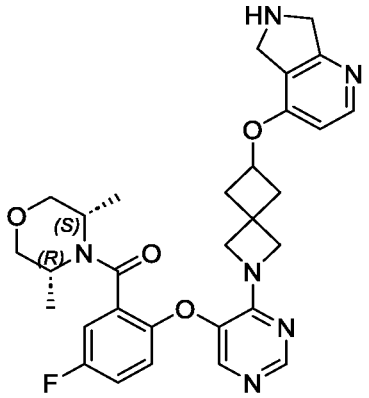
Step 5. tert-Butyl 4-((2-(5-(2-((3S,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 21, step 1, starting with 1.5 equivalents of *tert*-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 1 equivalent of (3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone and 4 equivalents of NaH were used. The reaction was stirred at 120 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(5-(2-((3*S*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a solid.

Yield: 55.5%; LCMS (Method D): Rt 1.97 min, m/z = 661.2 $[M+H]^+$, 58.08%.

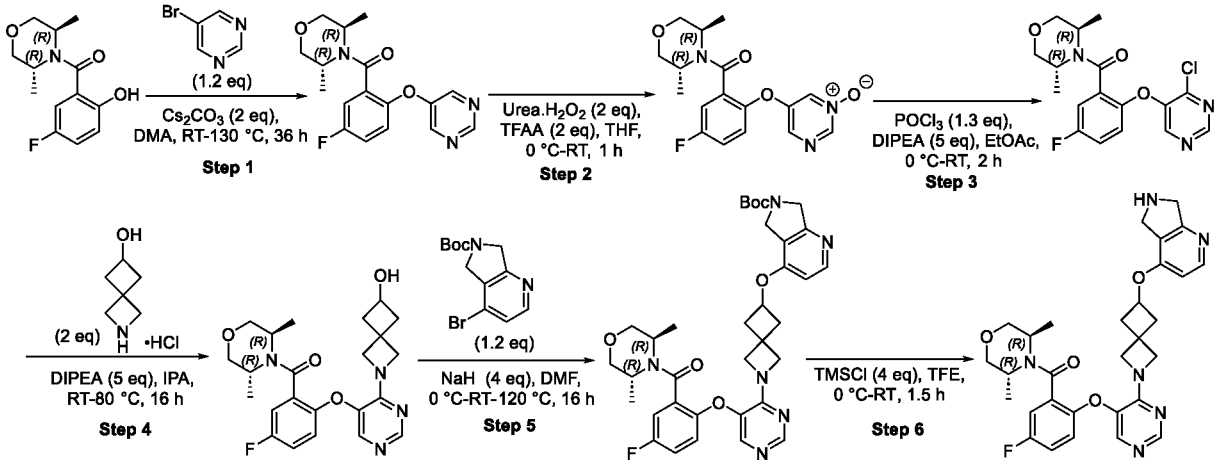
Step 6. (2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3S,5R)-3,5-dimethylmorpholino)methanone



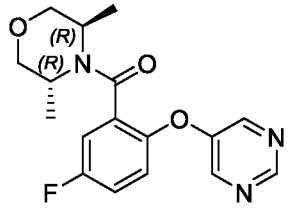
This compound was synthesized following the procedure described for the synthesis of Example 21, step 2, starting with *tert*-butyl 4-((2-(5-(2-((3*S*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to obtain crude (2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*S*,5*R*)-3,5-dimethylmorpholino)methanone hydrochloride. The crude was purified by Prep HPLC (Method S) to obtain (2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*S*,5*R*)-3,5-dimethylmorpholino)methanone as a solid.

Yield: 35.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 - 8.25 (m, 1H), 8.21 (d, J = 5.7 Hz, 1H), 7.84 - 7.66 (m, 1H), 7.47 - 7.32 (m, 1H), 7.32 - 7.22 (m, 1H), 7.10 - 6.98 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.87 - 4.69 (m, 1H), 4.50 - 4.07 (m, 6H), 4.03 (br s, 2H), 3.99 (br s, 2H), 3.79 - 3.51 (m, 4H), 2.83 - 2.75 (m, 2H), 2.31 - 2.17 (m, 2H), 1.38 - 1.27 (m, 6H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.06 min, m/z = 561.2 $[M+H]^+$; HPLC (Method A): Rt = 4.11 min, 99.26%.

Example 91. (2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone (Compound No. 24)



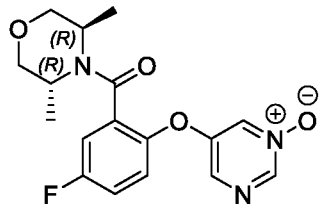
Step 1. (3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-(pyrimidin-5-yloxy)phenyl)methanone



This compound was synthesized following the procedure described for the synthesis of Example 90, step 1, starting with 1.2 equivalent of 5-bromo-pyrimidine, except that 1 equivalent of (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 50% EtOAc in hexane) to obtain (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-(pyrimidin-5-yloxy)phenyl)methanone as a solid.

Yield: 63.2%; LCMS (Method D): Rt = 1.42 min, m/z; 332.0 $[M+H]^+$, 96.53%.

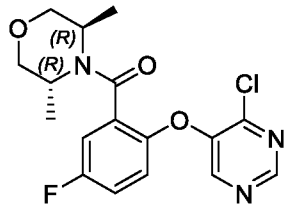
Step 2. 5-(2-((3R,5R)-3,5-Dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidine 1-oxide



This compound was synthesized following the procedure described for the synthesis of Example 90, step 2, starting with (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-(pyrimidin-5-yloxy)phenyl)methanone, except that 2 equivalents of TFAA was used to obtain 5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidine 1-oxide as a semi-solid. This material was used without further purification.

Yield: 66.1%; LCMS (Method D): Rt = 1.29 min, m/z; 348.1 $[M+H]^+$, 65.01%.

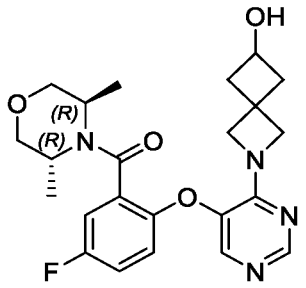
Step 3. (2-((4-Chloropyrimidin-5-yl)oxy)-5-fluorophenyl)((3R,5R)-3,5-dimethylmorpholino)methanone



This compound was synthesized following the procedure described for the synthesis of Example 90, step 3, starting with 5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidine 1-oxide, except that 1.3 equivalents of $POCl_3$ and 5 equivalents of DIPEA were used. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain (2-((4-chloropyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone as a semi-solid.

Yield: 54.9% yield; LCMS (Method D): Rt = 1.65 min, m/z = 366.0 $[M+H]^+$, 92.45%.

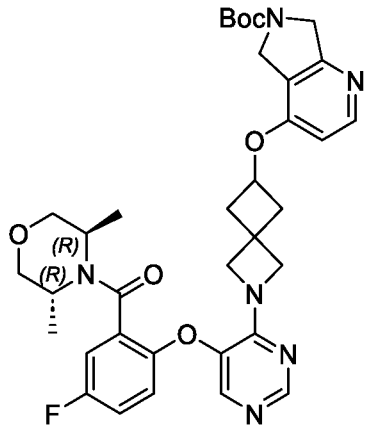
Step 4. ((3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone



This compound was synthesized following the procedure described for the synthesis of Example 90, step 4, starting with (2-((4-chloropyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone. The reaction was stirred at 80 °C for 16 h under conventional heating. The crude was purified by silica gel flash column chromatography using MeOH and DCM (product was eluted at 7% MeOH in DCM) to obtain ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone as a semi-solid.

Yield; 74.8%; LCMS (Method D): Rt = 1.38 min, m/z = 443.0 $[M+H]^+$, 90.45%.

Step 5. tert-Butyl 4-((2-(5-(2-((3R,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate

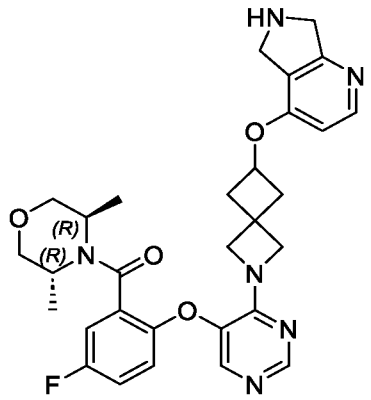


This compound was synthesized following the procedure described for the synthesis of Example 21, step 1, starting with 1.2 equivalents of tert-butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 1 equivalent of (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone was used. The reaction was stirred at 120 °C to obtain crude *tert*-butyl 4-((2-(5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-

4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate as a semi-solid.

Yield: 65%; LCMS (Method D): Rt = 1.90 min, m/z = 661.2 $[M+H]^+$, 64.74%. This material was used without further purification.

Step 6. (2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((*3R,5R*)-3,5-dimethylmorpholino)methanone

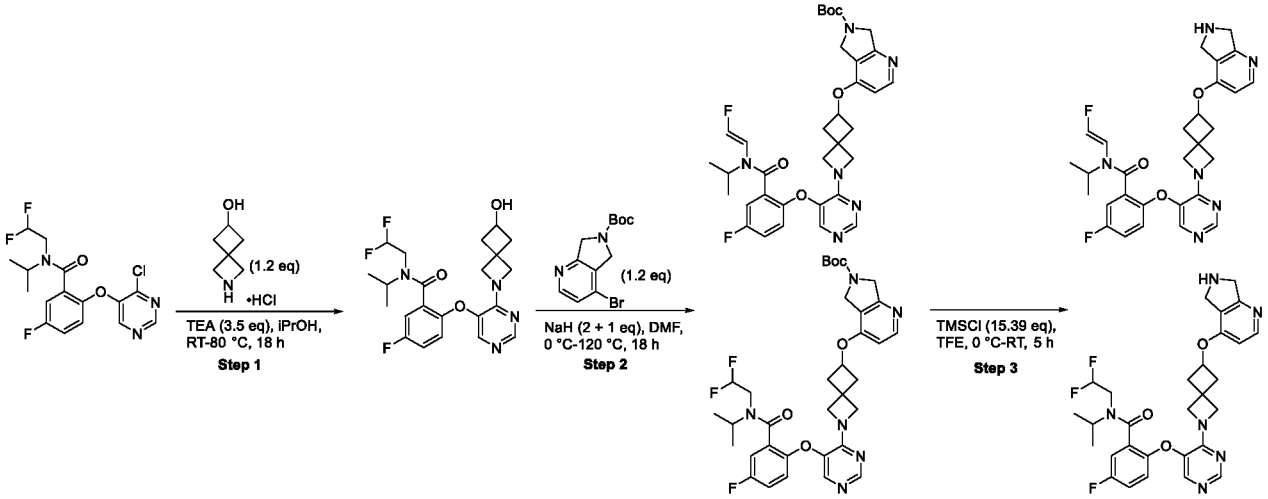


This compound was synthesized following the procedure described for the synthesis of Example 21, step 2, starting with *tert*-butyl 4-((2-(5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone hydrochloride. The crude was purified by Prep HPLC (Method AG) to obtain (2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone as a solid.

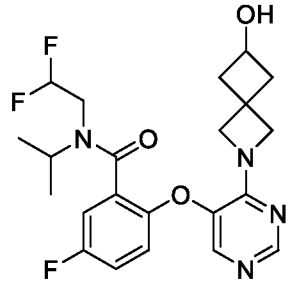
Yield: 42.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.22 (d, *J* = 5.7 Hz, 1H), 7.71 (s, 1H), 7.41 - 7.35 (m, 1H), 7.33 - 7.26 (m, 1H), 7.05 (dd, *J* = 4.4, 9.1 Hz, 1H), 6.70 (d, *J* = 5.7 Hz, 1H), 4.84 - 4.71 (m, 1H), 4.30 - 4.11 (m, 4H), 4.07 - 3.99 (m, 4H), 3.97 - 3.39 (m, 6H), 2.84 - 2.74 (m, 2H), 2.32 - 2.22 (m, 2H), 1.22 (br s, 6H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.45 min; m/z = 561.3 $[M+H]^+$; HPLC (Method A): Rt = 4.10 min, 98.17%; Chiral SFC (Method E): Rt = 2.47 min, 100%.

Example 92. *N*-(2,2-Difluoroethyl)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 15)

Example 93. 2-((4-(6-((6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-(2-fluorovinyl)-*N*-isopropylbenzamide (Compound No. 18)



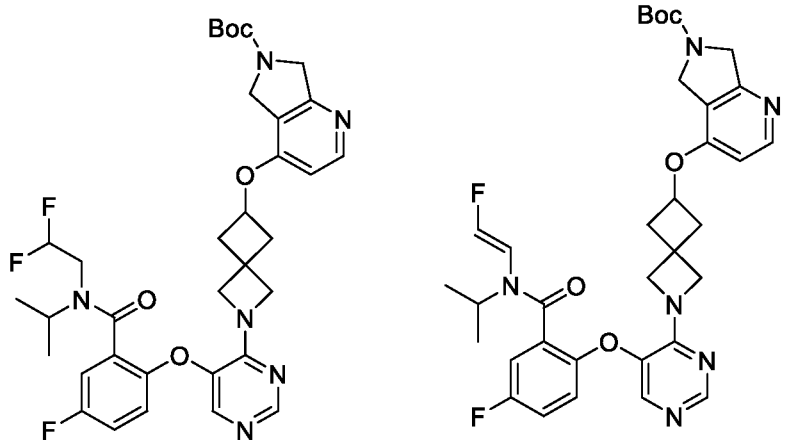
Step 1. N-(2,2-Difluoroethyl)-5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



In a dried, 50 mL round bottom flask under a nitrogen atmosphere, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (500 mg, 1.338 mmol) was added in 2-propanol (10 mL). To this reaction mixture, 2-azaspiro[3.3]heptan-6-ol hydrochloride (240 mg, 1.605 mmol), and TEA (0.653 mL, 4.68 mmol) were added at RT. The reaction was stirred at 80 °C for 18 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (520 mg, 63.3% yield) as a solid. LCMS (Method H): Rt = 1.30 min, m/z = 451.2 $[M+H]^+$; 73.30%.

Step 2. tert-Butyl 4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and (E)-tert-butyl-4-((2-(5-(4-fluoro-2-((2-

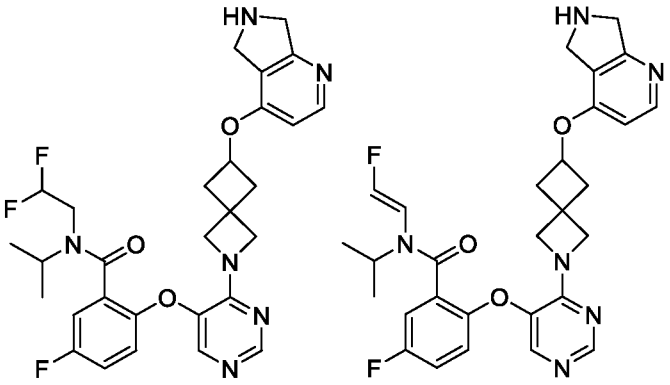
fluorovinyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



In a dried, 50 mL two-neck round bottom flask under a nitrogen atmosphere, *N*-(2,2-difluoroethyl)-5-fluoro-2-((4-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (250 mg, 0.555 mmol) was added in DMF (10 mL). NaH (44.4 mg, 1.110 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 30 min. *tert*-Butyl 4-bromo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (199 mg, 0.666 mmol) was added to the reaction at RT, and the reaction was stirred at 120 °C for 18 h. Based on the TLC, the reaction was not completed. Therefore, another lot of NaH (22.20 mg, 0.555 mmol) was added to the reaction at 0 °C. The reaction was continued to stir at 120 °C for another 18 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM) to obtain a mixture of *tert*-butyl 4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and (E)-*tert*-butyl-4-((2-(5-(4-fluoro-2-((2-fluorovinyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (170 mg, 21.97% yield). LCMS (Method H): Peak 1: Rt = 1.71 min, m/z = 649.2 $[M+H]^+$; 13.38%; Peak 2: Rt = 1.75 min, m/z = 669.3 $[M+H]^+$; 47.96%.

Step 3. N-(2,2-Difluoroethyl)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide and (E)-2-((4-

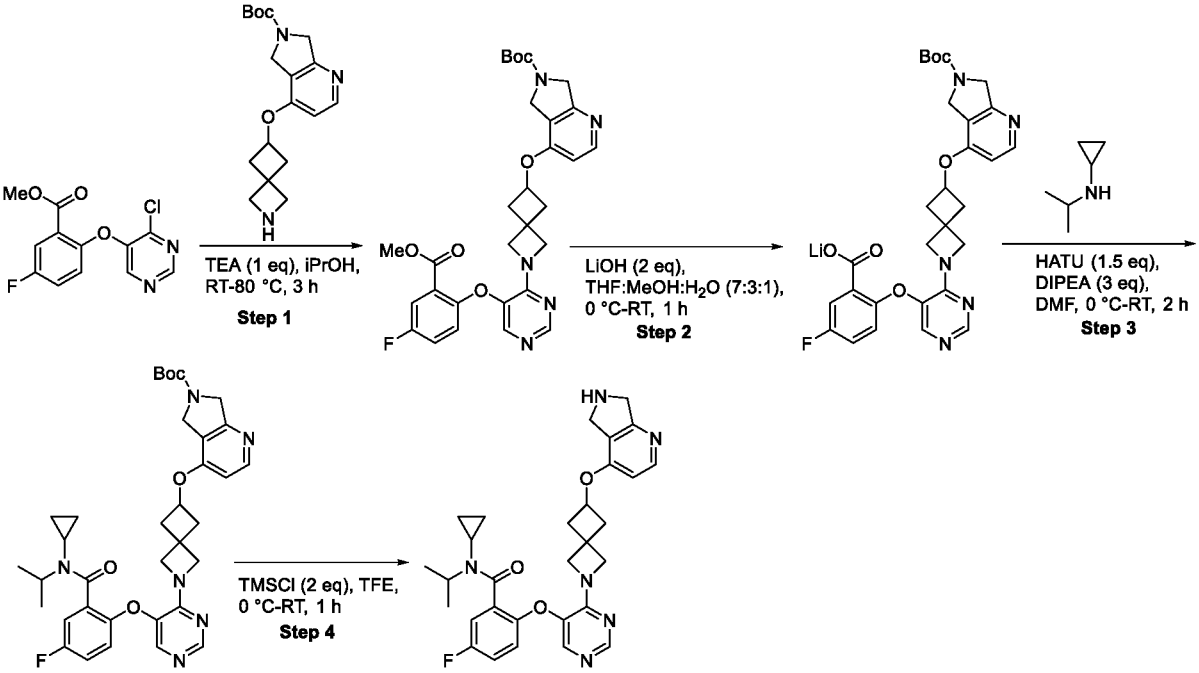
(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-(2-fluorovinyl)-N-isopropylbenzamide



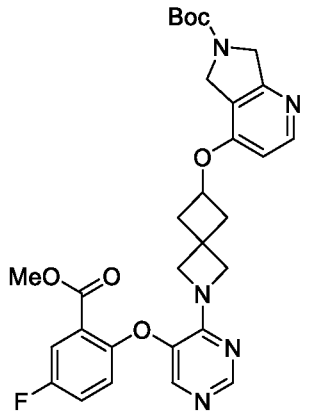
In a dried, 50 mL round bottom flask under a nitrogen atmosphere, a mixture of *tert*-butyl 4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and *(E)-tert*-butyl-4-((2-(5-(4-fluoro-2-((2-fluorovinyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate (170 mg, 0.254 mmol) was added in 2,2,2-trifluoroethanol (5 mL). TMSCl (0.5 mL, 3.91 mmol) was added to this solution at 0 °C and stirred at RT for 5 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method I) to obtain *N*-(2,2-difluoroethyl)-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (16.57 mg, 11.14% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.21 (d, J = 5.6 Hz, 1H), 7.81 (s, 1H), 7.35 (dd, J = 3.1, 8.2 Hz, 1H), 7.33 - 7.22 (m, 1H), 7.01 (dd, J = 4.2, 9.1 Hz, 1H), 6.68 (d, J = 5.8 Hz, 1H), 6.39 - 6.07 (m, 1H), 4.81 - 4.73 (m, 1H), 4.43 (br s, 1H), 4.30 - 4.06 (m, 4H), 4.03 (s, 2H), 3.99 (s, 2H), 3.91 - 3.81 (m, 1H), 3.80 - 3.66 (m, 2H), 2.80 - 2.76 (m, 2H), 2.30 - 2.25 (m, 2H), 1.25 - 1.04 (m, 6H); LCMS (Method D): Rt = 1.60 min, m/z = 569.2 $[M+H]^+$; HPLC (Method A): Rt = 4.54 min, 97.16% and 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-(2-fluorovinyl)-*N*-isopropylbenzamide (10.5 mg, 7.04% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.21 (d, J = 5.6 Hz, 1H), 7.72 - 7.65 (m, 1H), 7.30 - 7.22 (m, 2H), 6.99 - 6.84 (m, 2H), 6.69 (d, J = 5.8 Hz, 1H), 5.83 - 5.69 (m, 1H), 4.85 - 4.63 (m, 2H), 4.43 (br s, 1H), 4.26 - 4.12 (m, 4H), 4.03 (s, 2H), 3.99 (s, 2H), 2.84 - 2.75 (m, 2H), 2.32 - 2.24 (m, 2H), 1.13 (d, J = 6.8 Hz, 6H); LCMS (Method D): Rt = 1.66 min, m/z = 549.1 $[M+H]^+$; HPLC (Method E): Rt = 3.01 min, 93.56%.

Example 94. ***N*-Cyclopropyl-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**

(Compound No. 48)



Step 1. tert-Butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate

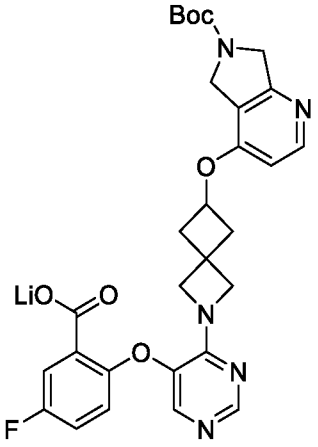


This compound was synthesized following the procedure described for the synthesis of Example 9, step 1, starting with methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate, except that 1 equivalent of *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate and 1 equivalent of Et_3N were used. The reaction was concentrated under reduced pressure. The crude was diluted with ice water and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using

MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate.

Yield: 28.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.28 (m, 2H), 7.70 - 7.63 (m, 2H), 7.52 - 7.45 (m, 1H), 7.15 - 7.07 (m, 1H), 6.81 (d, J = 5.8 Hz, 1H), 4.83 (quin, J = 6.7 Hz, 1H), 4.55 - 4.44 (m, 4H), 4.27 (s, 2H), 4.18 (s, 2H), 3.81 (s, 3H), 2.84 - 2.75 (m, 2H), 2.35 - 2.26 (m, 2H), 1.46 (s, 9H); LCMS (Method D): Rt = 2.05 min, m/z = 578.2 $[M+H]^+$; 72.94%.

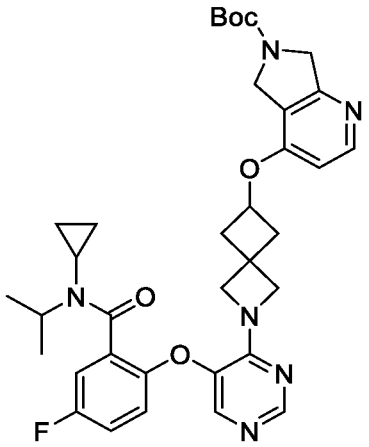
Step 2. Lithium 2-((4-(6-((6-(tert-butoxycarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 2, starting with *tert*-butyl 4-((2-(5-(4-fluoro-2-(methoxycarbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 2 equivalents of LiOH was used in THF:MeOH:H_2O (7:3:1) as a solvent. The reaction was concentrated under reduced pressure to obtain crude lithium 2-((4-(6-((6-(*tert*-butoxycarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate.

Yield: 91%; LCMS (Method D): Rt = 1.42 min, m/z = 564.5 $[M+H]^+$; 95.34%. This material was used without further purification.

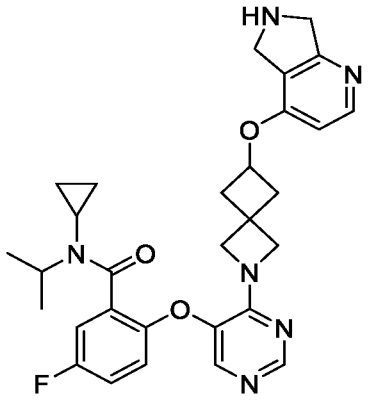
Step 3. tert-Butyl 4-((2-(5-(2-(cyclopropyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of lithium 2-((4-(6-((6-(*tert*-butoxycarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate and 1 equivalent of *N*-isopropylcyclopropanamine. The reaction was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(cyclopropyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate.

Yield: 79%; LCMS (Method B): Rt = 2.10 min, m/z = 645.3 $[M+H]^+$; 89.21%.

Step 4. N-Cyclopropyl-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide

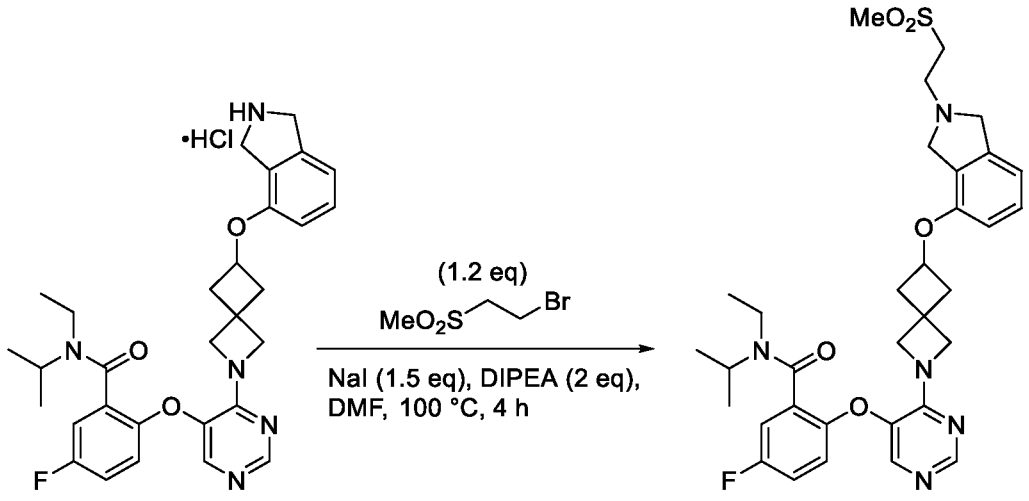


This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl 4-((2-(5-(2-(cyclopropyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate, except that 2 equivalents of TMSCl was used and 2,2,2-

trifluoroethanol was used as a solvent. The reaction was concentrated under reduced pressure to obtain *N*-cyclopropyl-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-cyclopropyl-2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide.

Yield: 22.29%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.21 (d, *J* = 5.7 Hz, 1H), 7.71 (s, 1H), 7.33 (dd, *J* = 3.0, 8.4 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.01 (dd, *J* = 4.5, 9.1 Hz, 1H), 6.69 (d, *J* = 5.8 Hz, 1H), 4.78 (quin, *J* = 6.7 Hz, 1H), 4.50 - 4.27 (m, 2H), 4.25 - 4.09 (m, 4H), 4.03 (s, 2H), 3.99 (s, 2H), 2.83 - 2.75 (m, 2H), 2.65 - 2.58 (m, 1H), 2.31 - 2.24 (m, 2H), 1.28 (d, *J* = 6.7 Hz, 6H), 0.53 (br s, 4H); LCMS (Method D): Rt = 1.66 min, m/z = 545.3 $[M+H]^+$; HPLC (Method A): Rt = 4.66 min, 99.92%.

Example 95. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-(2-(methylsulfonyl)ethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 29)

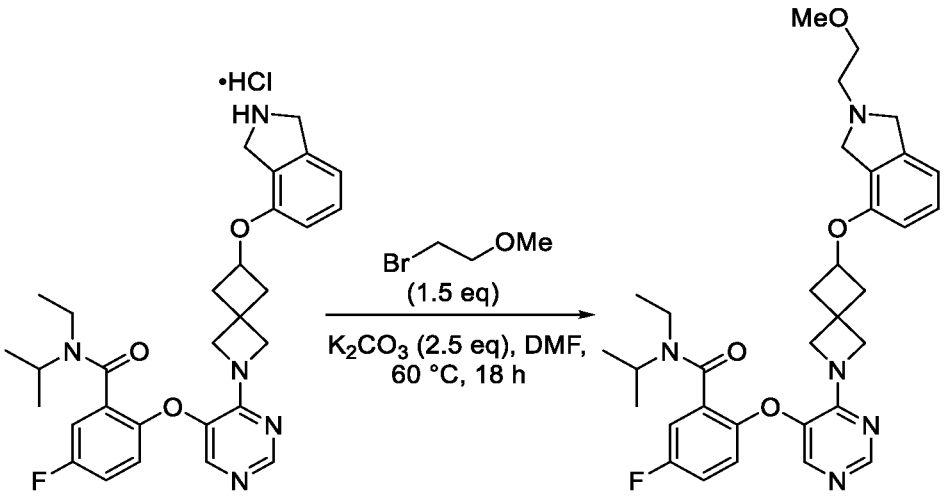


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride and 1.2 equivalents of 1-bromo-2-(methylsulfonyl)ethane, except that 2 equivalents of DIPEA and 1.5 equivalents of sodium iodide were used, and DMF was used as a solvent. The reaction was stirred in a pressure vial at 100 °C. The reaction was poured into water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was

purified by Prep HPLC (Method N) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-(2-(methylsulfonyl)ethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 30.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 7.78 - 7.66 (m, 1H), 7.34 - 7.21 (m, 2H), 7.18 - 6.99 (m, 2H), 6.81 (d, J = 7.4 Hz, 1H), 6.69 - 6.63 (m, 1H), 4.71 - 4.62 (m, 1H), 4.46 - 4.07 (m, 4H), 3.91 (s, 2H), 3.85 (s, 2H), 3.80 - 3.70 (m, 1H), 3.44 - 3.41 (m, 1H), 3.27 - 3.22 (m, 1H), 3.12 - 3.06 (m, 2H), 3.02 (s, 3H), 2.78 - 2.70 (m, 2H), 2.28 - 2.17 (m, 2H), 1.25 - 0.98 (m, 9H); two protons merged with solvent peaks; LCMS (Method D): Rt = 1.81 min, m/z = 638.2 $[M+H]^+$; HPLC (Method A): Rt = 5.79 min, 99.57%.

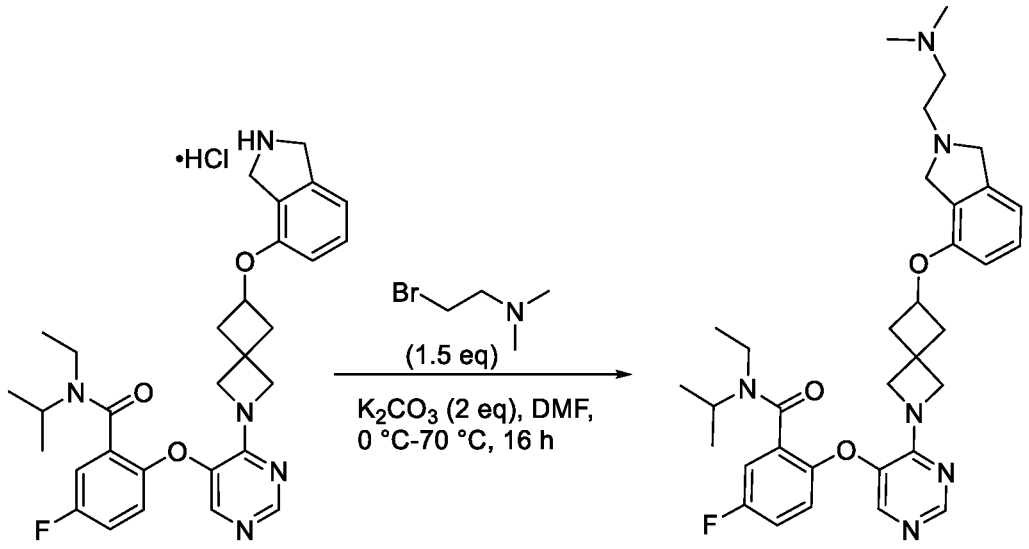
Example 96. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-(2-methoxyethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 36)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride and 1.5 equivalents of bromo-2-methoxyethane, except that 2.5 equivalents of K_2CO_3 was used, and DMF was used as a solvent. The reaction was stirred at 60 °C. After completion, the reaction was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude compound was purified by Prep HPLC (Method AI), then by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-(2-methoxyethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 3.41%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.23 (m, 1H), 7.78 - 7.64 (m, 1H), 7.34 - 7.21 (m, 2H), 7.16 - 7.00 (m, 2H), 6.80 (d, J = 7.4 Hz, 1H), 6.67 - 6.61 (m, 1H), 4.72 - 4.60 (m, 1H), 4.30 - 4.05 (m, 4H), 3.86 (s, 2H), 3.80 (s, 2H), 3.78 - 3.72 (m, 1H), 3.48 (t, J = 5.9 Hz, 2H), 3.45 - 3.35 (m, 1H), 3.27 (s, 3H), 3.25 - 3.10 (m, 1H), 2.82 (t, J = 5.9 Hz, 2H), 2.79 - 2.69 (m, 2H), 2.27 - 2.18 (m, 2H), 1.31 - 0.95 (m, 9H); LCMS (Method B): Rt = 1.72 min, m/z = 590.6 $[M+H]^+$; HPLC (Method A): Rt = 6.01 min, 99.46%.

Example 97. 2-((4-(6-((2-(2-(Dimethylamino)ethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 37)

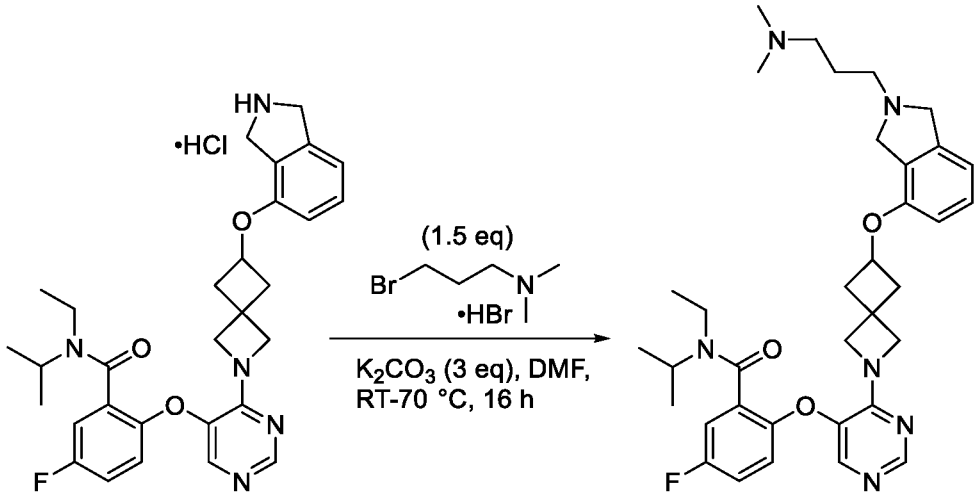


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride and 1.5 equivalents of 2-bromo-*N*,*N*-dimethylethan-1-amine, except that 2 equivalents of K_2CO_3 was used, and DMF was used as a solvent. The reaction was poured into ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method B) to afford 2-((4-(6-((2-(2-(dimethylamino)ethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 7.16%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.15 - 6.99 (m, 2H), 6.80 (d, J = 7.4 Hz, 1H), 6.67 - 6.59 (m, 1H), 4.70 - 4.61 (m, 1H), 4.46 - 4.07 (m, 4H), 3.84 (s, 2H), 3.78 (s, 2H), 3.76 - 3.70 (m, 1H), 3.44 - 3.39 (m, 1H), 3.25 - 3.12 (m, 1H), 2.78 - 2.70 (m, 4H), 2.41 - 2.36 (m, 2H), 2.27 - 2.19 (m, 2H),

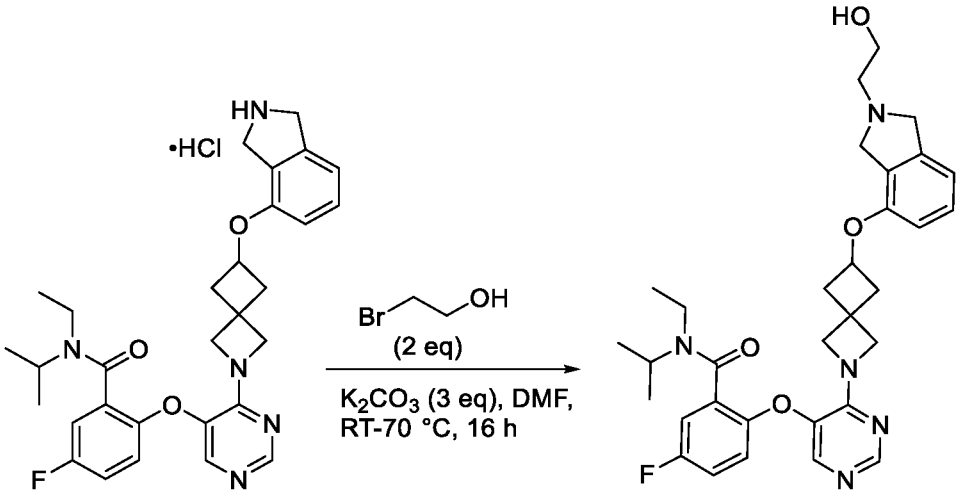
2.17 (s, 6H), 1.22 - 0.96 (m, 9H); LCMS (Method J): Rt = 1.32 min, m/z = 603.4 $[M+H]^+$; HPLC (Method F): Rt = 5.49 min, 96.68%.

Example 98. 2-((4-(6-((2-(3-(Dimethylamino)propyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 38)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride and 1.5 equivalents of 3-bromo-*N*,*N*-dimethylpropan-1-amine hydrobromide, except that 3 equivalents of K_2CO_3 was used, and DMF was used as a solvent. The reaction was added to ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method Q) and lyophilized to afford 2-((4-(6-((2-(3-(dimethylamino)propyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide. Yield: 2.34%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 7.77 - 7.64 (m, 1H), 7.32 - 7.21 (m, 2H), 7.14 - 6.99 (m, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 4.72 - 4.61 (m, 1H), 4.43 - 4.08 (m, 4H), 3.81 (s, 2H), 3.78 - 3.71 (m, 3H), 3.45 - 3.38 (m, 1H), 3.26 - 3.20 (m, 1H), 2.78 - 2.69 (m, 2H), 2.64 (br t, *J* = 7.3 Hz, 2H), 2.30 - 2.18 (m, 4H), 2.13 (s, 6H), 1.61 (quin, *J* = 7.2 Hz, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.81 min, m/z = 617.4 $[M+H]^+$; HPLC (Method A): Rt = 5.67 min, 99.27%.

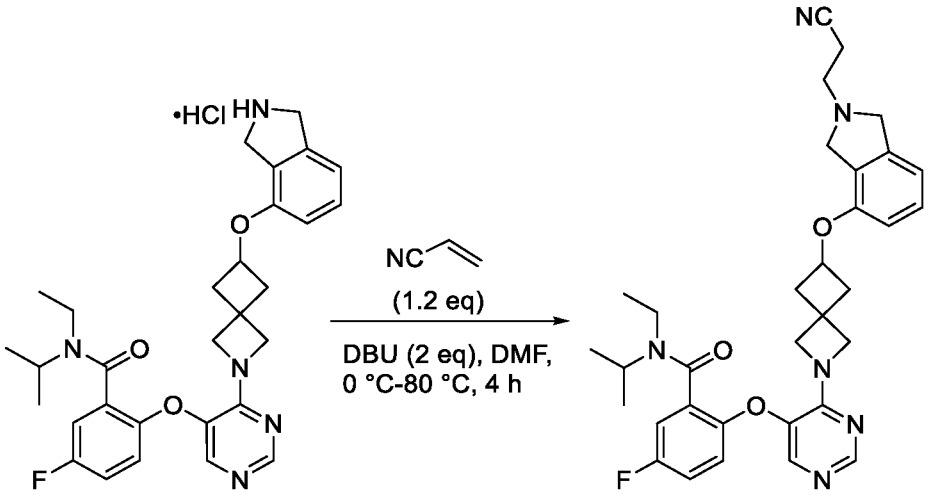
Example 99. *N*-Ethyl-5-fluoro-2-((4-(6-((2-(2-hydroxyethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 42)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride and 2 equivalents of 2-bromoethan-1-ol, except that 3 equivalents of K_2CO_3 was used, and DMF was used as a solvent. The reaction was added to ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method B) to afford *N*-ethyl-5-fluoro-2-((4-(6-((2-(2-hydroxyethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

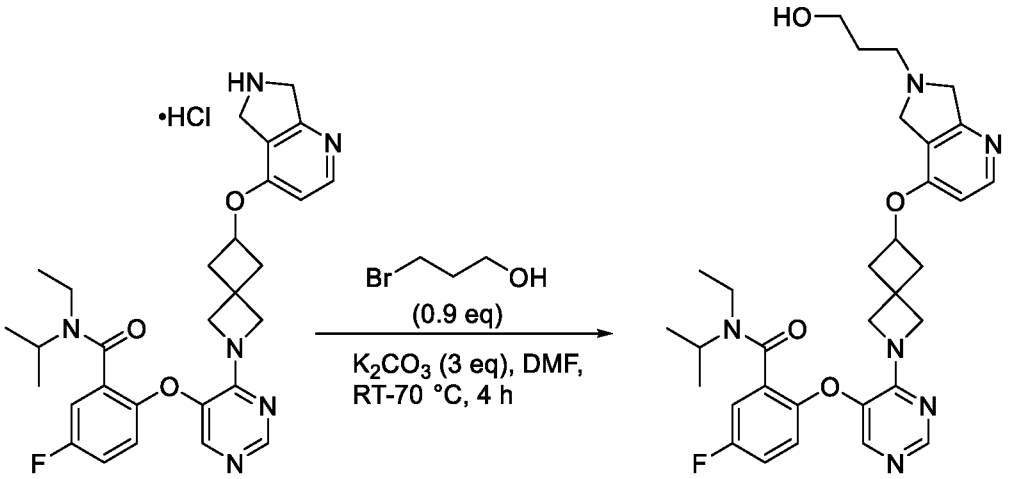
Yield: 30.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.15 - 7.00 (m, 2H), 6.80 (d, J = 7.4 Hz, 1H), 6.66 - 6.61 (m, 1H), 4.70 - 4.61 (m, 1H), 4.49 (t, J = 5.5 Hz, 1H), 4.46 - 4.08 (m, 4H), 3.87 (s, 2H), 3.81 (s, 2H), 3.79 - 3.70 (m, 1H), 3.54 (q, J = 6.1 Hz, 2H), 3.45 - 3.36 (m, 1H), 3.29 - 3.12 (m, 1H), 2.79 - 2.71 (m, 4H), 2.27 - 2.18 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.68 min, m/z = 576.3 $[M+H]^+$; HPLC (Method A): Rt = 5.39 min, 99.49%.

Example 100. 2-((4-(6-((2-(2-Cyanoethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 34)



In an 8 mL pressure vial under a nitrogen atmosphere, *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride (190 mg, 0.334 mmol) and acrylonitrile (21.30 mg, 0.401 mmol) were added in DMF (5 mL). DBU (102 mg, 0.669 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at 80 °C for 4 h. The reaction was poured into water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM). An impure product (117 mg-HPLC-95.4%) was obtained. Therefore, the product was re-purified by Prep HPLC (Method B) to afford 2-((4-(6-((2-(2-cyanoethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (72.7 mg, 36.9%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.10 - 7.00 (m, 1H), 6.82 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 4.72 - 4.63 (m, 1H), 4.47 - 4.07 (m, 4H), 3.90 (s, 2H), 3.84 (s, 2H), 3.81 - 3.69 (m, 1H), 3.44 - 3.37 (m, 1H), 3.28 - 3.13 (m, 1H), 2.94 - 2.89 (m, 2H), 2.79 - 2.71 (m, 4H), 2.29 - 2.18 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.94 min, m/z = 585.3 $[M+H]^+$; HPLC (Method A): Rt = 6.06 min, 99.29%.

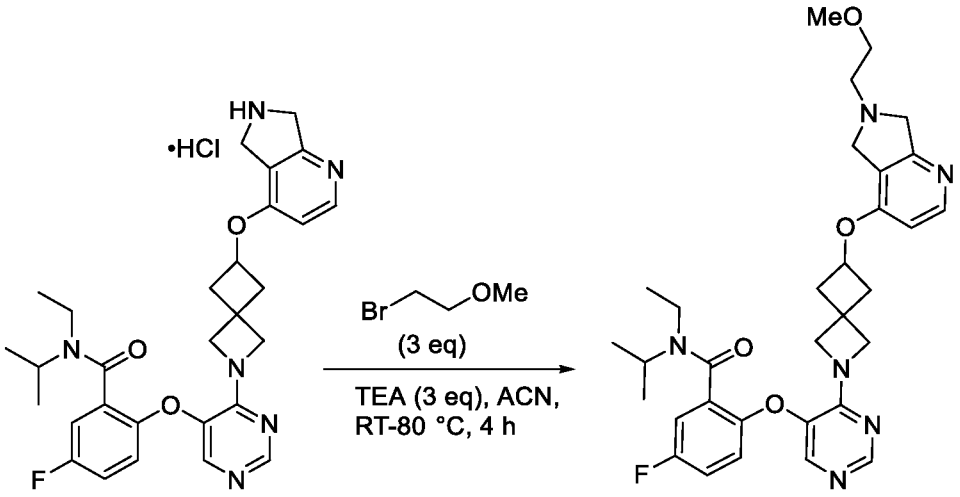
Example 101. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxypropyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 51)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 0.9 equivalent of 3-bromopropan-1-ol, except that 3 equivalents of K_2CO_3 was used, and DMF was used as a solvent. The reaction was added to ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method D) to afford *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxypropyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 7.24%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.22 - 8.18 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.74 - 6.69 (m, 1H), 4.83 - 4.74 (m, 1H), 4.46 - 4.39 (m, 1H), 4.30 - 4.07 (m, 4H), 3.80 (s, 4H), 3.78 - 3.70 (m, 1H), 3.48 (q, J = 6.1 Hz, 2H), 3.43 - 3.37 (m, 1H), 3.27 - 3.14 (m, 1H), 2.80 - 2.76 (m, 2H), 2.71 (t, J = 7.2 Hz, 2H), 2.31 - 2.22 (m, 2H), 1.65 (quin, J = 6.7 Hz, 2H), 1.22 - 0.98 (m, 9H); LCMS (Method D): Rt = 1.61 min, m/z = 591.2 $[M+H]^+$; HPLC (Method A): Rt = 4.72 min, 99.30%.

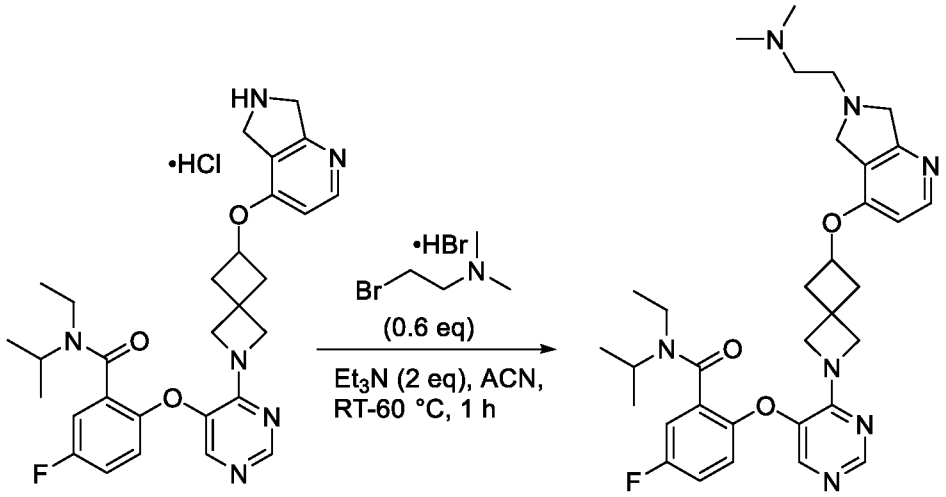
Example 102. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxyethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 43)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 3 equivalents of 1-bromo-2-methoxyethane, except that 3 equivalents of TEA was used. The reaction was stirred at 80 °C. The reaction was added to ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxyethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 15.77%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.22 - 8.18 (m, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 6.99 (m, 1H), 6.74 - 6.69 (m, 1H), 4.83 - 4.72 (m, 1H), 4.46 - 4.08 (m, 4H), 3.86 (s, 4H), 3.80 - 3.70 (m, 1H), 3.49 (t, *J* = 5.8 Hz, 2H), 3.45 - 3.37 (m, 1H), 3.27 (s, 3H), 3.25 - 3.13 (m, 1H), 2.85 (t, *J* = 5.8 Hz, 2H), 2.81 - 2.73 (m, 2H), 2.31 - 2.22 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.78 min, m/z = 591.7 $[M+H]^+$; HPLC (Method A): Rt = 5.12 min, 96.45%.

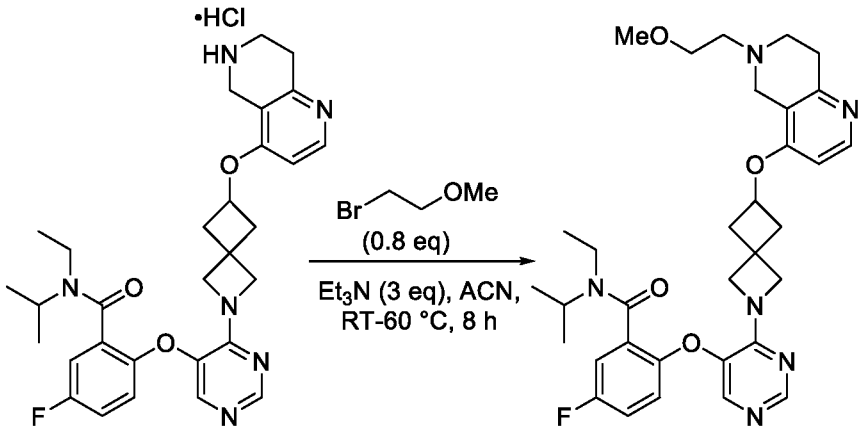
Example 103. 2-((4-(6-((6-(2-(Dimethylamino)ethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 46)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 0.6 equivalent of 2-bromo-*N*,*N*-dimethylethan-1-amine hydrobromide, except that 2 equivalents of TEA were used. The reaction was stirred in a pressure vial at 60 °C. The crude product was purified by Prep HPLC (Method AD) to afford 2-((4-(6-((6-(2-(dimethylamino)ethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 8.32%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 - 8.18 (m, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.09 - 7.00 (m, 1H), 6.72 - 6.69 (m, 1H), 4.82 - 4.73 (m, 1H), 4.46 - 4.07 (m, 4H), 3.84 (s, 4H), 3.80 - 3.73 (m, 1H), 3.45 - 3.37 (m, 1H), 3.26 - 3.13 (m, 1H), 2.80 - 2.73 (m, 4H), 2.42 - 2.37 (m, 2H), 2.31 - 2.21 (m, 2H), 2.17 (s, 6H), 1.22 - 0.93 (m, 9H); LCMS (Method D): Rt = 1.73 min, m/z = 604.4 $[M+H]^+$; HPLC (Method A): Rt = 4.92 min, 95.35%.

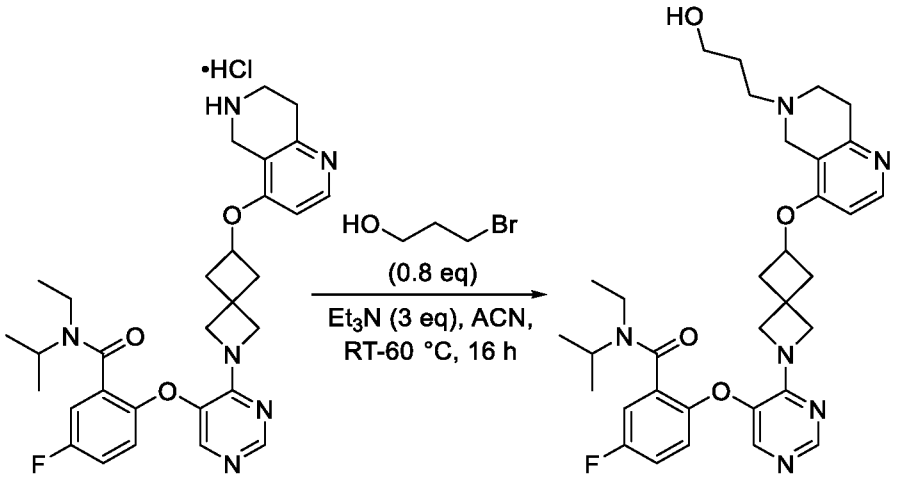
Example 104. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 60)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 1-bromo-2-methoxyethane, except that 3 equivalents of TEA was used. The reaction was stirred at 60 °C. The crude compound was purified by Prep HPLC (Method C) to afford *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 18.17%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.79 - 7.63 (m, 1H), 7.35 - 7.20 (m, 2H), 7.11 - 6.99 (m, 1H), 6.71 - 6.61 (m, 1H), 4.80 - 4.69 (m, 1H), 4.34 - 4.03 (m, 4H), 3.75 (sep, J = 6.6 Hz, 1H), 3.50 (t, J = 5.8 Hz, 2H), 3.47 (s, 2H), 3.43 - 3.37 (m, 1H), 3.26 (s, 3H), 3.23 - 3.08 (m, 1H), 2.84 - 2.71 (m, 6H), 2.71 - 2.64 (m, 2H), 2.31 - 2.18 (m, 2H), 1.36 - 0.87 (m, 9H); LCMS (Method D): Rt = 1.74 min, m/z = 605.4 $[M+H]^+$; HPLC (Method A): Rt = 5.56 min, 99.18%.

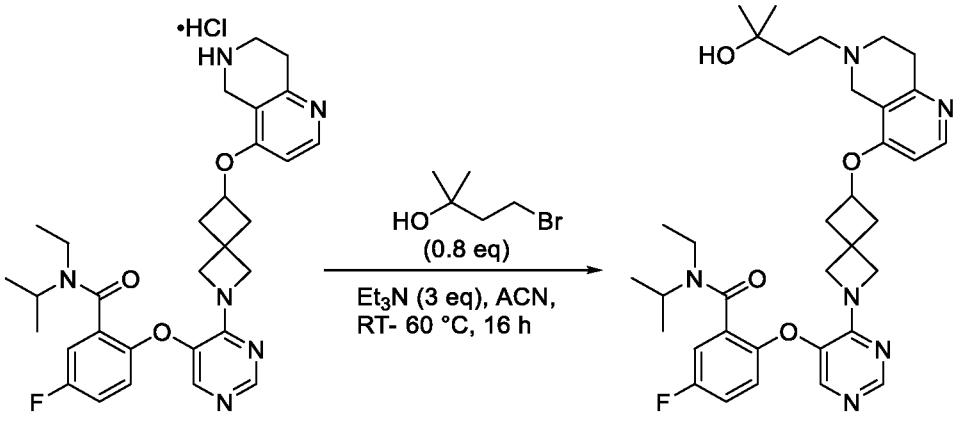
Example 105. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 62)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 3-bromopropan-1-ol, except that 3 equivalents of TEA was used. The reaction was stirred at 60 °C. The crude compound was purified by Prep HPLC (Method AG) to afford *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 25.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.81 - 4.69 (m, 1H), 4.48 - 4.39 (m, 1H), 4.32 - 4.07 (m, 4H), 3.76 (sep, *J* = 6.6 Hz, 1H), 3.51 - 3.37 (m, 5H), 3.29 - 3.06 (m, 1H), 2.85 - 2.74 (m, 4H), 2.71 - 2.64 (m, 2H), 2.59 - 2.53 (m, 2H), 2.32 - 2.22 (m, 2H), 1.66 (quin, *J* = 6.7 Hz, 2H), 1.30 - 0.95 (m, 9H); LCMS (Method D): Rt = 1.61 min, m/z = 605.4 $[M+H]^+$; HPLC (Method A): Rt = 5.11 min, 97.41%.

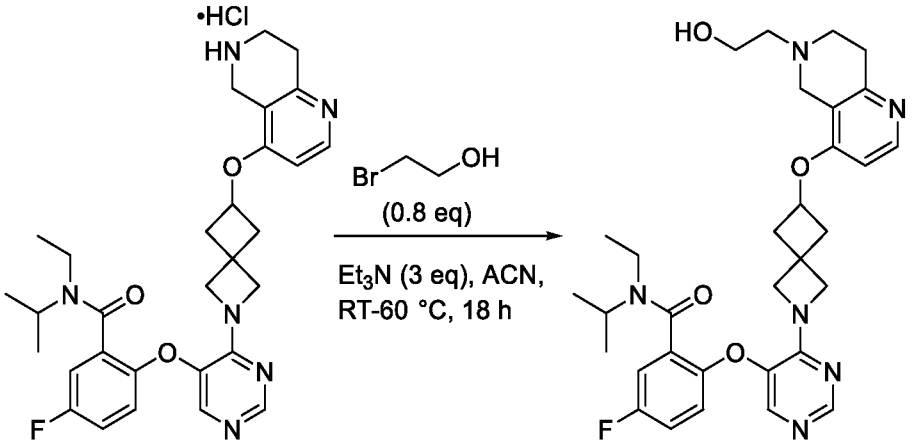
Example 106. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxy-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 63)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 4-bromo-2-methylbutan-2-ol, except that 3 equivalents of Et_3N was used. The crude was purified by Prep HPLC (Method B) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-hydroxy-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 13.74%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.14 - 6.94 (m, 1H), 6.67 (d, J = 5.7 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.50 (br s, 1H), 4.33 - 4.07 (m, 4H), 3.84 - 3.69 (m, 1H), 3.51 - 3.36 (m, 3H), 3.29 - 3.06 (m, 1H), 2.86 - 2.72 (m, 4H), 2.74 - 2.67 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.41 - 2.20 (m, 2H), 1.61 (t, J = 7.6 Hz, 2H), 1.29 - 0.93 (m, 15H); LCMS (Method D): Rt = 1.75 min, m/z = 633.4 $[M+H]^+$; HPLC (Method A): Rt = 5.57 min, 99.79%.

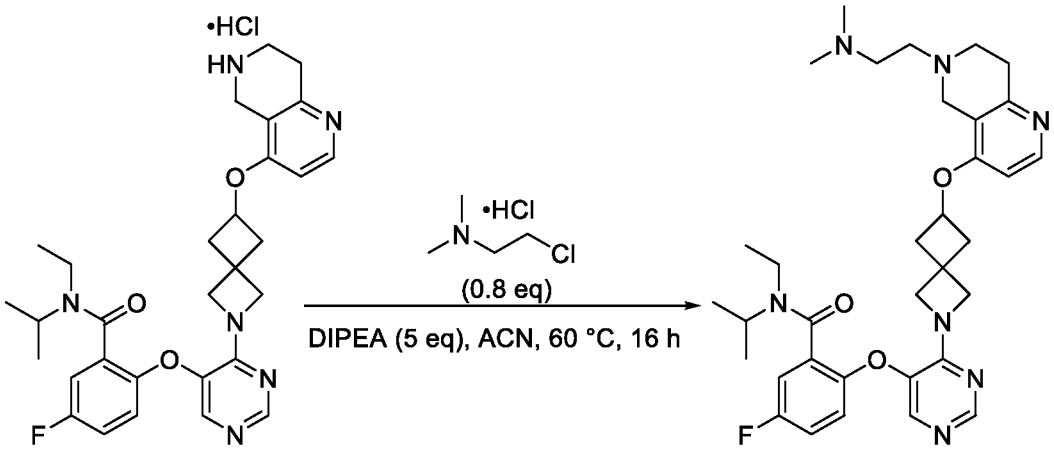
Example.107.*N*-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 66)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 2-bromoethan-1-ol, except that 3 equivalents of TEA was used. The reaction was stirred at 60 °C. The crude compound was purified by Prep HPLC (Method AH) to afford *N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 13.33%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.81 - 7.62 (m, 1H), 7.34 - 7.19 (m, 2H), 7.12 - 7.00 (m, 1H), 6.70 - 6.60 (m, 1H), 4.81 - 4.68 (m, 1H), 4.45 (t, J = 5.3 Hz, 1H), 4.34 - 4.04 (m, 4H), 3.76 (spt J = 6.5 Hz, 1H), 3.57 (q, J = 5.9 Hz, 2H), 3.48 (s, 2H), 3.44 - 3.37 (m, 1H), 3.29 - 3.10 (m, 1H), 2.87 - 2.70 (m, 6H), 2.59 (t, J = 6.1 Hz, 2H), 2.31 - 2.21 (m, 2H), 1.38 - 0.91 (m, 9H); LCMS (Method D): Rt = 1.65 min, m/z = 591.4 $[M+H]^+$, 99.89% ; HPLC (Method A): Rt = 5.03 min, 99.68%.

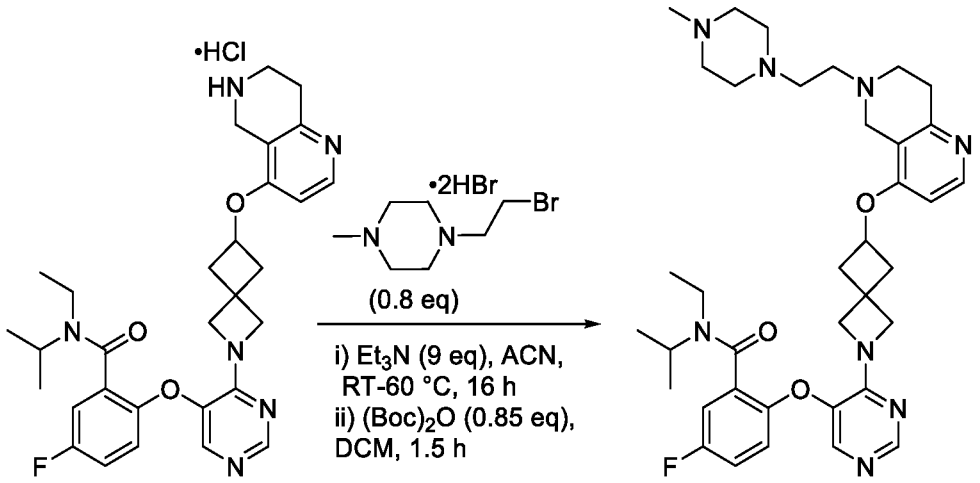
Example 108. 2-((4-(6-((6-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 69)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 2-chloro-*N*,*N*-dimethylethan-1-amine hydrochloride, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C for 16 h. The crude was purified Prep HPLC (Method J) to obtain 2-((4-(6-((6-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 6.86%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.78 - 7.64 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.65 (m, 1H), 4.79 - 4.69 (m, 1H), 4.48 - 4.04 (m, 4H), 3.82 - 3.69 (m, 1H), 3.46 (br s, 2H), 3.44 - 3.37 (m, 2H), 3.27 - 3.13 (m, 2H), 2.85 - 2.69 (m, 6H), 2.64 - 2.57 (m, 2H), 2.30 - 2.23 (m, 2H), 2.20 (s, 6H), 1.15 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.63 min, m/z = 618.4 $[M+H]^+$; HPLC (Method A): Rt = 4.97 min, 98.18%.

Example 109. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylpiperazin-1-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 70)

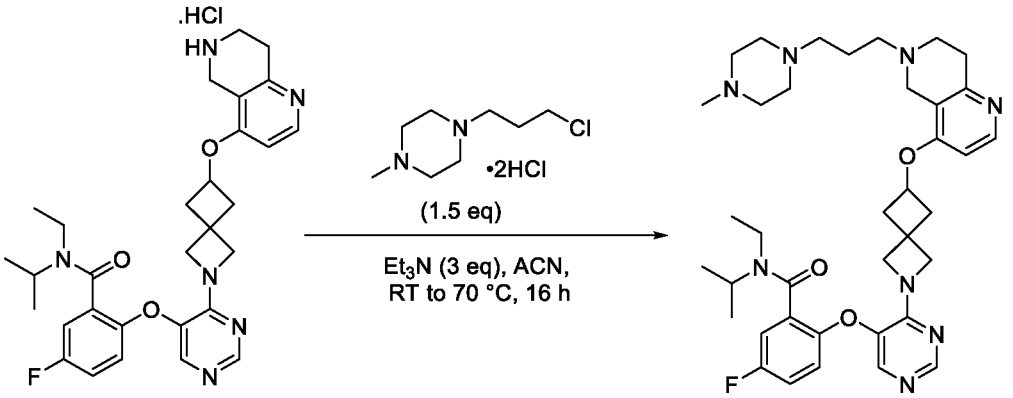


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 1-(2-bromoethyl)-4-methylpiperazine dihydrobromide, except that 9 equivalents of TEA was used. The reaction was stirred at 60 °C. The progress of the reaction was monitored by TLC (10% MeOH in DCM). The crude LCMS and HPLC showed the starting material and product were in the same peak. Therefore, the unreacted starting material was protected with a Boc group following the below procedure.

The reaction was concentrated under reduced pressure and dissolved in DCM, then $(Boc)_2O$ (0.85 equivalent) was added at 0 °C. The reaction was stirred at RT for 1.5 h. The progress was monitored by TLC (10%MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method AF) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylpiperazin-1-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 4.51%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 - 8.24 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.80 - 7.64 (m, 1H), 7.35 - 7.21 (m, 2H), 7.13 - 6.98 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.80 - 4.69 (m, 1H), 4.31 - 4.07 (m, 4H), 3.81 - 3.65 (m, 1H), 3.49 (s, 2H), 3.44 - 3.38 (m, 1H), 3.27 - 3.10 (m, 2H), 2.85 - 2.69 (m, 7H), 2.64 - 2.58 (m, 4H), 2.46 - 2.39 (m, 4H), 2.31 - 2.21 (m, 4H), 2.14 (s, 3H), 1.35 - 0.95 (m, 9H); LCMS (Method B): Rt = 1.30 min, m/z = 673.4 $[M+H]^+$; HPLC (Method A): Rt = 4.66 min, 98.29%.

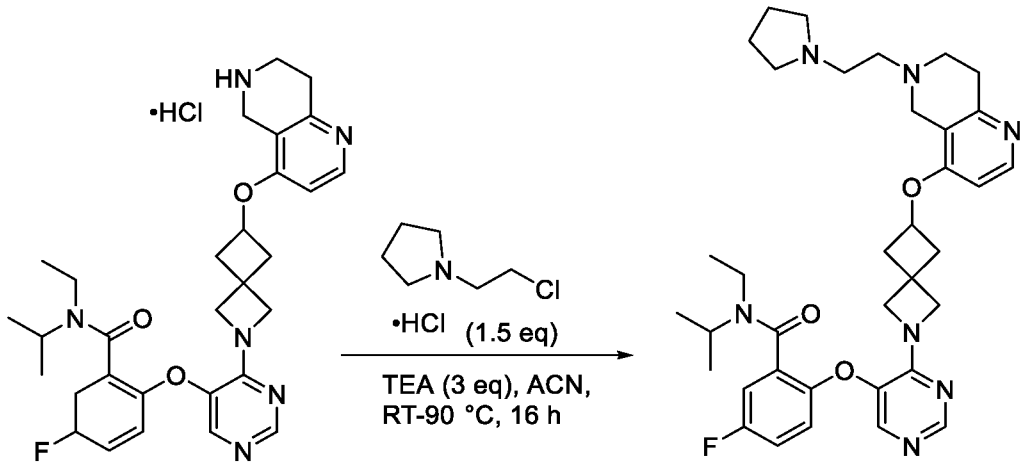
Example 110. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 71)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.5 equivalents of 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride, except that 3 equivalents of TEA was used. The progress of the reaction was monitored by TLC (10% MeOH in DCM). The crude LCMS and HPLC showed the starting material and product were in the same peak. Therefore, the unreacted starting material was protected with a Boc group following the below procedure to make the purification easier.

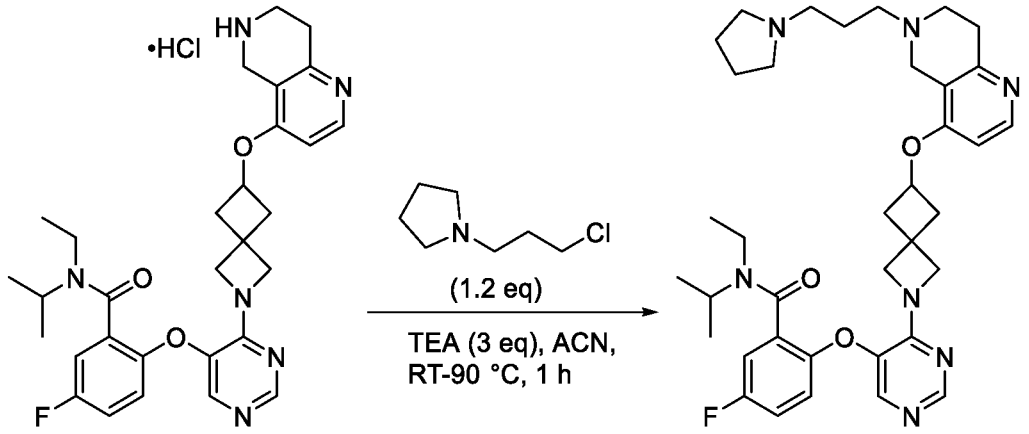
The reaction was concentrated under reduced pressure and DCM was added. To this reaction mixture, $(Boc)_2O$ (0.2 equivalent) and TEA (3 equivalents) were added at 0 °C. The reaction was stirred at RT for 1 h. The progress was monitored by TLC (10%MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (44.05 mg, 23.34% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.26 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.79 - 7.64 (m, 1H), 7.36 - 7.20 (m, 2H), 7.11 - 6.97 (m, 1H), 6.66 (d, J = 5.5 Hz, 1H), 4.83 - 4.67 (m, 1H), 4.34 - 4.06 (m, 4H), 3.83 - 3.68 (m, 1H), 3.48 - 3.37 (m, 4H), 3.27 - 3.07 (m, 2H), 2.85 - 2.73 (m, 4H), 2.71 - 2.63 (m, 2H), 2.43 - 2.20 (m, 12H), 2.14 (s, 3H), 1.64 (quin, J = 7.1 Hz, 2H), 1.29 - 0.92 (m, 9H); LCMS (Method D): Rt = 1.64 min, m/z = 687.4 $[M+H]^+$; HPLC (Method A): Rt = 4.78 min, 99.74%.

Example 111. ***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(pyrrolidin-1-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 79)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.5 equivalents of 1-(2-chloroethyl)pyrrolidine hydrochloride, except that 3 equivalents of TEA was used. The reaction was stirred at 90 °C. The reaction was concentrated under reduced pressure, the residue was diluted with water, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine solution, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method A) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(pyrrolidin-1-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide. Yield: 9.33%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.19 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.67 (m, 1H), 4.46 - 4.07 (m, 4H), 3.82 - 3.69 (m, 1H), 3.49 - 3.39 (m, 3H), 3.24 - 3.12 (m, 2H), 2.83 - 2.70 (m, 6H), 2.62 (s, 4H), 2.31 - 2.17 (m, 2H), 1.72 - 1.63 (m, 4H), 1.21 - 0.97 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.71 min, m/z = 644.6 $[M+H]^+$; HPLC (Method A): Rt = 5.13 min, 98.54%.

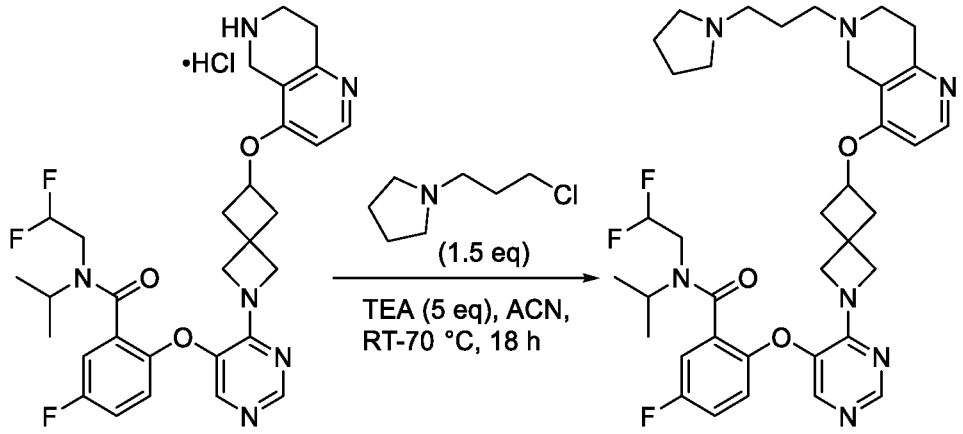
Example 112. ***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 81)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.2 equivalents of 1-(3-chloropropyl)pyrrolidine, except that 3 equivalents of TEA was used. The reaction was stirred at 90 °C. The reaction was concentrated under reduced pressure, the residue was diluted with water, and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 19.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.68 - 6.63 (m, 1H), 4.79 - 4.70 (m, 1H), 4.47 - 4.08 (m, 4H), 3.81 - 3.67 (m, 1H), 3.44 - 3.37 (m, 3H), 3.28 - 3.12 (m, 2H), 2.84 - 2.65 (m, 6H), 2.45 - 2.39 (m, 6H), 2.31 - 2.21 (m, 2H), 1.72 - 1.63 (m, 6H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.68 min, m/z = 658.6 $[M+H]^+$; HPLC (Method A): Rt = 4.75 min, 98.23%.

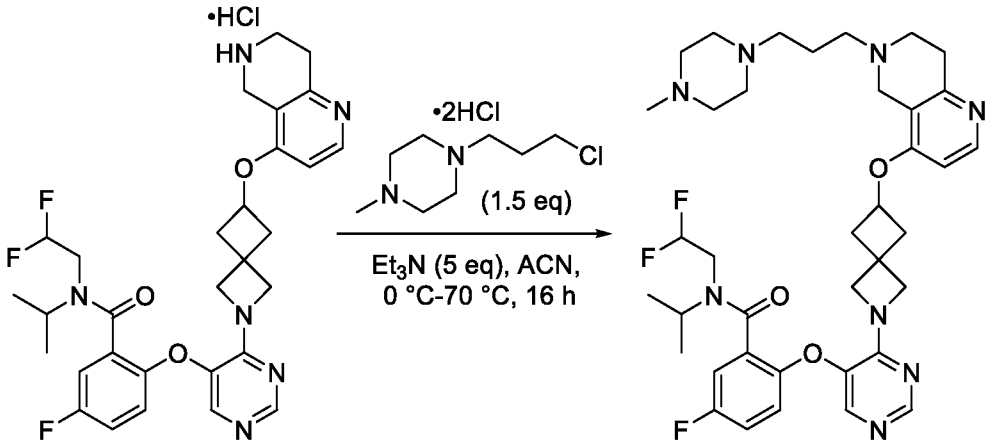
Example 113. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 97)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.5 equivalents of 1-(3-chloropropyl)pyrrolidine, except that 5 equivalents of TEA was used. The reaction was stirred in a pressure vial. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 22.62%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.28 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.83 - 7.70 (m, 1H), 7.35 (dd, J = 3.1, 8.3 Hz, 1H), 7.29 (dt, J = 3.1, 8.6 Hz, 1H), 7.06 - 6.99 (m, 1H), 6.65 (d, J = 5.8 Hz, 1H), 6.40 - 6.06 (m, 1H), 4.78 - 4.67 (m, 1H), 4.35 - 4.05 (m, 4H), 3.91 - 3.80 (m, 1H), 3.79 - 3.66 (m, 2H), 3.40 (s, 2H), 2.83 - 2.67 (m, 6H), 2.40 (t, J = 6.7 Hz, 6H), 2.30 - 2.21 (m, 2H), 1.71 - 1.62 (m, 6H), 1.26 - 1.04 (m, 6H), two protons merged with solvent peaks; LCMS (Method A): Rt = 2.78 min, m/z = 694.3 $[M+H]^+$; HPLC (Method A): Rt = 5.37 min, 96.09%.

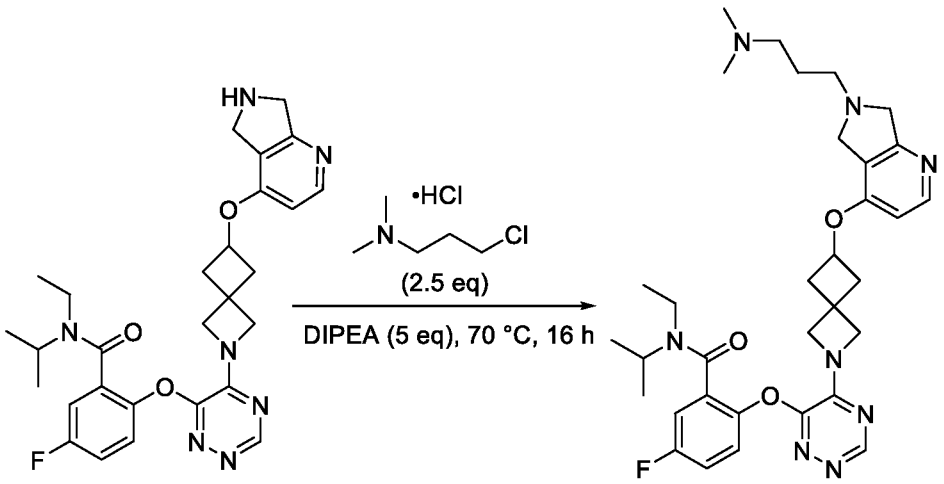
Example.114. ***N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 98)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with of 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.5 equivalents of 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride, except that 5 equivalents of TEA was used. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 36.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.40 - 7.25 (m, 2H), 7.01 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.8 Hz, 1H), 6.42 - 6.04 (m, 1H), 4.73 (quin, J = 6.6 Hz, 1H), 4.30 - 4.03 (m, 4H), 3.85 (sep, J = 6.8 Hz, 1H), 3.80 - 3.62 (m, 2H), 3.40 (s, 2H), 2.83 - 2.71 (m, 4H), 2.71 - 2.63 (m, 3H), 2.42 - 2.20 (m, 12H), 2.14 (s, 3H), 1.71 - 1.56 (m, 2H), 1.29 - 0.98 (m, 6H). One proton merged with solvent peaks; LCMS (Method B): Rt = 1.34 min, m/z = 723.3 $[M+H]^+$; HPLC (Method A): Rt = 5.03 min, 94.50%.

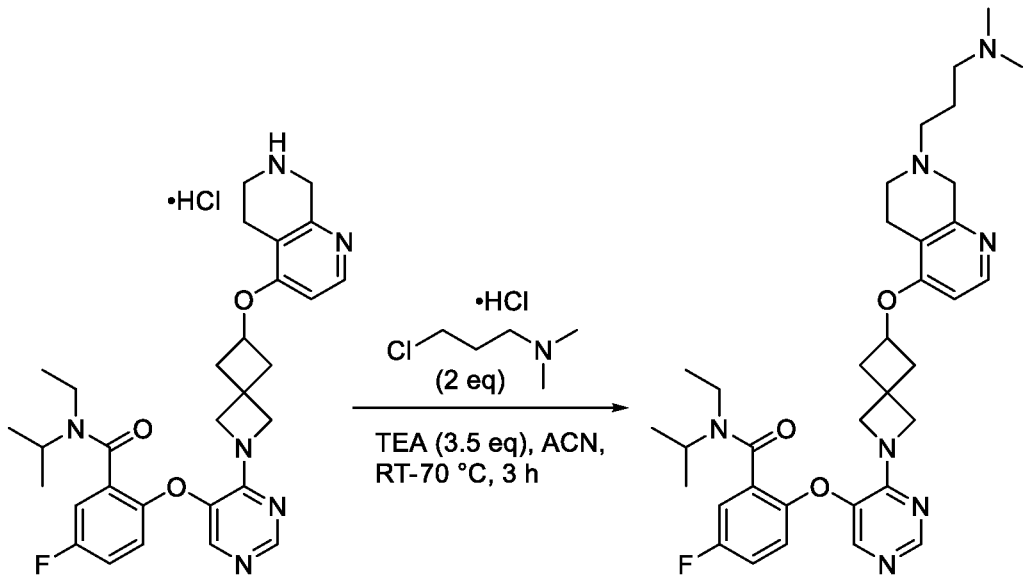
Example 115. 2-((5-(6-((6-(3-(Dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 296)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of 2-((5-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2.5 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride, except that 5 equivalents of DIPEA was used. The crude was purified by Prep HPLC (Method F) to obtain 2-((5-(6-((6-(3-(dimethylamino)propyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 24.55%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.22 (d, J = 5.7 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.73 (d, J = 5.8 Hz, 1H), 4.88 - 4.78 (m, 1H), 4.69 - 4.48 (m, 2H), 4.33 - 4.09 (m, 2H), 3.81 (s, 4H), 3.67 - 3.58 (m, 1H), 3.15 - 2.98 (m, 2H), 2.88 - 2.77 (m, 2H), 2.71 - 2.62 (m, 2H), 2.38 - 2.22 (m, 4H), 2.12 (s, 6H), 1.67 - 1.57 (m, 2H), 1.16 - 0.66 (m, 9H); LCMS (Method G): Rt = 1.60 min, m/z = 619.4 $[M+H]^+$; HPLC (Method A): Rt = 4.44 min, 97.87%.

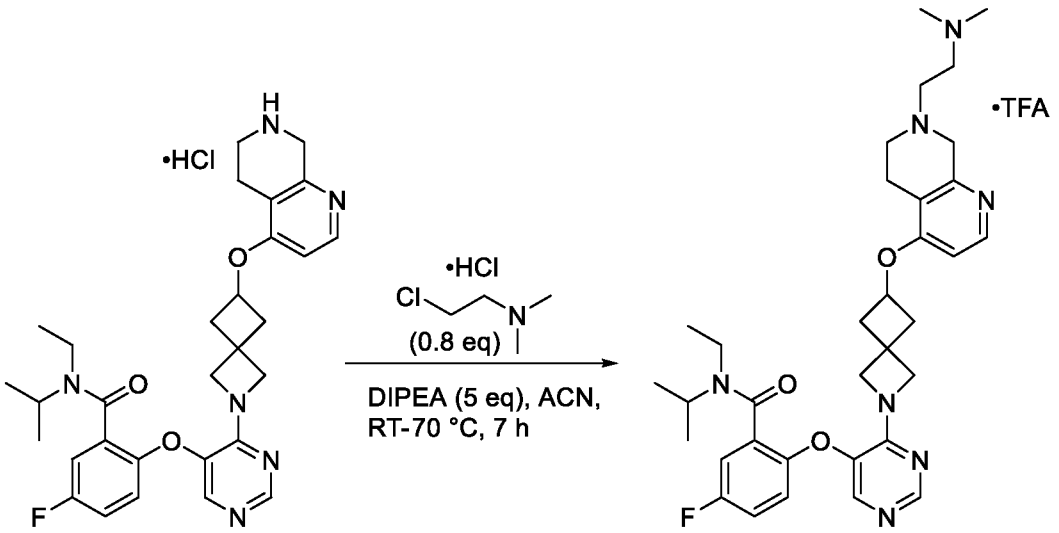
Example 116. 2-((4-(6-((7-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 116)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 2 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride, except that 3.5 equivalents of TEA was used. The reaction was stirred in a pressure vial. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The impure product was re-purified by Prep HPLC (Method B) to afford 2-((4-(6-((7-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 12.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.78 - 7.67 (m, 1H), 7.33 - 7.21 (m, 2H), 7.09 - 6.99 (m, 1H), 6.69 - 6.65 (m, 1H), 4.79 - 4.70 (m, 1H), 4.44 - 4.08 (m, 4H), 3.80 - 3.72 (m, 1H), 3.48 (s, 2H), 3.43 - 3.40 (m, 1H), 3.25 - 3.16 (m, 1H), 2.81 -2.75 (m, 2H), 2.61 (s, 6H), 2.30 - 2.18 (m, 4H), 2.12 (s, 6H), 1.63 (quin, J = 7.2 Hz, 2H), 1.25 - 0.98 (m, 9H); LCMS (Method J): Rt = 1.49 min, m/z = 632.3 $[M+H]^+$; HPLC (Method E): Rt = 2.97 min, 99.17%.

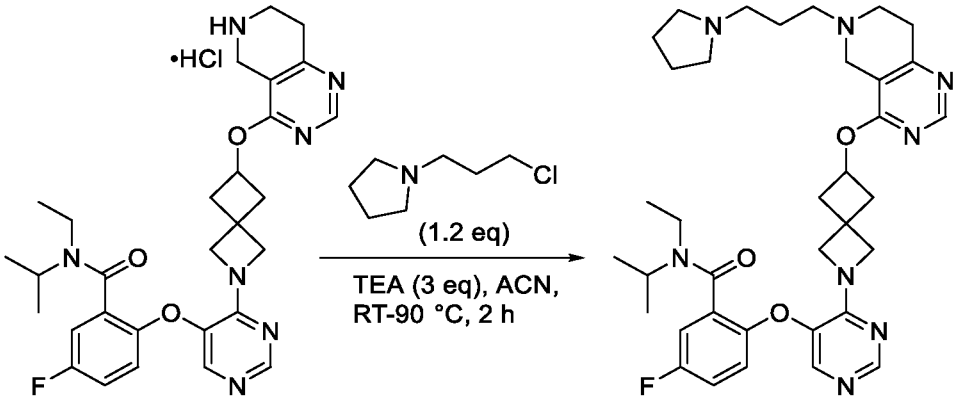
Example 117. 2-((4-(6-((7-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide 2,2,2-trifluoroacetate (Compound No. 125-a)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 0.8 equivalent of 2-chloro-*N*,*N*-dimethylethan-1-amine hydrochloride, except that 5 equivalents of DIPEA was used. The reaction was stirred in a pressure vial. The reaction was concentrated under reduced pressure, and the residue was re-concentrated from DCM. The crude product was purified by Prep HPLC (Method O). The fractions were concentrated to obtain the desired product as a sticky solid (TFA salt). The compound was diluted with cold water, washed with saturated sodium bicarbonate, and then extracted with 20% MeOH in DCM. The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and lyophilized to afford 2-((4-(6-((7-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide 2,2,2-trifluoroacetate.

Yield: 7.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.77 - 7.68 (m, 1H), 7.34 - 7.21 (m, 2H), 7.09 - 6.99 (m, 1H), 6.69 - 6.65 (m, 1H), 4.79 - 4.70 (m, 1H), 4.46 - 4.07 (m, 4H), 3.80 - 3.70 (m, 1H), 3.57 (s, 2H), 3.46 - 3.40 (m, 1H), 3.24 - 3.14 (m, 1H), 2.81 - 2.74 (m, 2H), 2.71 - 2.61 (m, 6H), 2.27 - 2.21 (m, 3H), 1.23 - 0.97 (m, 9H), seven protons merged with solvent peaks; ^{19}F NMR (377 MHz, DMSO-d_6): δ -73.40 (s, 3F), -118.64 (s, 1F); LCMS (Method G): Rt = 1.67 min, m/z = 618.6 $[M+H]^+$; HPLC (Method A): Rt = 5.57 min, 96.96%.

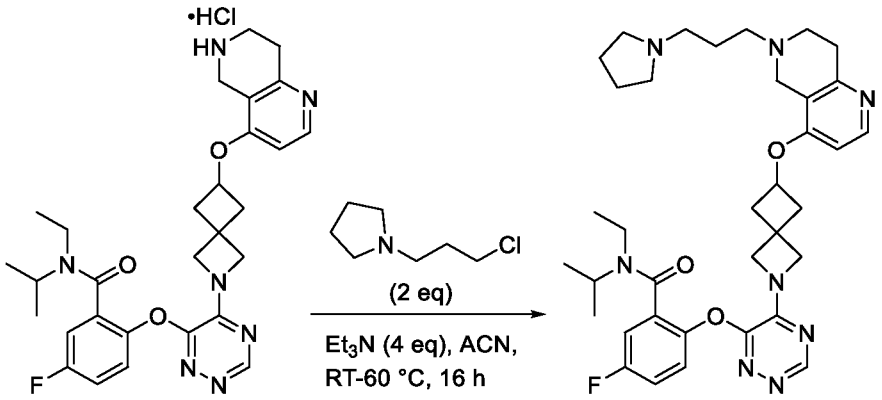
Example 118. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 94)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.2 equivalents of 1-(3-chloropropyl)pyrrolidine, except that 3 equivalents of Et_3N was used. The reaction was stirred in a pressure vial at 90 °C. The reaction was diluted with water and extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain pure product (lot 1, HPLC-98.07%) and impure product. The impure product was re-purified by Prep HPLC (Method P) to obtain the pure product (lot 2, HPLC-97.68%) as a solid. Both lots were combined to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 11.04%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 8.31 - 8.26 (m, 1H), 7.77 - 7.67 (m, 1H), 7.33 - 7.21 (m, 2H), 7.09 - 6.97 (m, 1H), 5.21 - 5.11 (m, 1H), 4.47 - 4.08 (m, 4H), 3.82 - 3.69 (m, 1H), 3.44 - 3.37 (m, 3H), 3.27 - 3.17 (m, 2H), 2.80 - 2.66 (m, 6H), 2.45 - 2.38 (m, 6H), 2.33 - 2.25 (m, 2H), 1.71 - 1.63 (m, 6H), 1.24 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method A): Rt = 2.26 min, m/z = 659.6 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 98.07%.

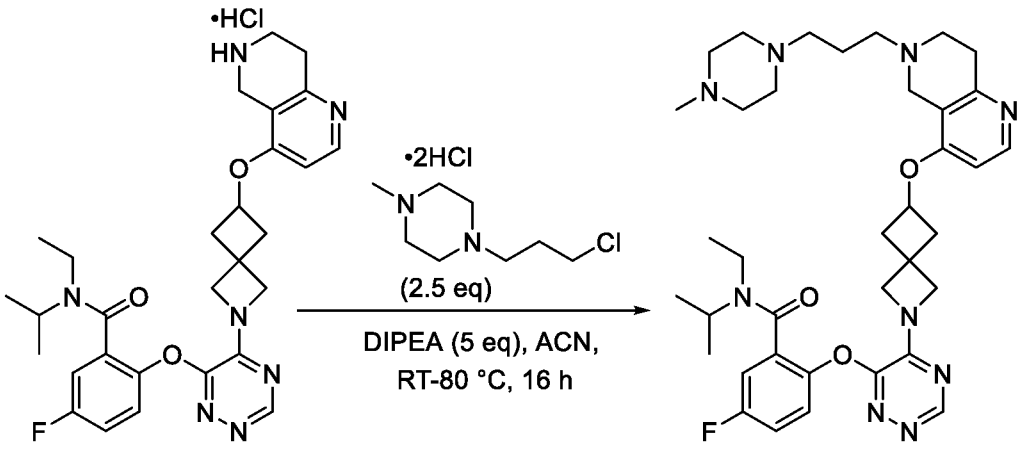
Example 119. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 112)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 2 equivalents of 1-(3-chloropropyl)pyrrolidine, except that 4 equivalents of Et_3N was used. The reaction was stirred at 60 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 16.80%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.7 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.39 - 7.30 (m, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.80-4.77 (m, 1H), 4.69 - 4.47 (m, 2H), 4.25 - 4.11 (m, 2H), 3.70 - 3.54 (m, 1H), 3.42 (br s, 2H), 3.31 - 3.21 (m, 2H), 3.18 - 2.98 (m, 1H), 2.88 - 2.77 (m, 4H), 2.70 - 2.60 (m, 2H), 2.45 - 2.27 (m, 9H), 1.72 - 1.66 (br s, 6H), 1.18 - 0.61 (m, 9H); LCMS (Method G): Rt = 1.61 min, m/z = 659.6 $[M+H]^+$; HPLC (Method A): Rt = 4.79 min, 98.72%.

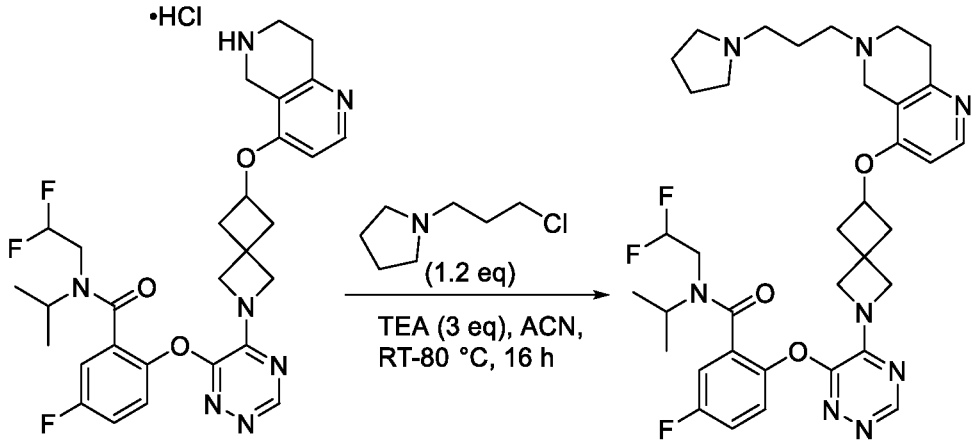
Example 120. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 113)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 2.5 equivalents of 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride, except that 5 equivalents of DIPEA was used. The reaction was stirred at 80 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 39.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.70-4.77 (m, 1H), 4.68 - 4.49 (m, 2H), 4.32 - 4.06 (m, 2H), 3.69 - 3.57 (m, 1H), 3.42 (s, 3H), 3.38 - 3.33 (m, 2H), 3.21 - 2.97 (m, 1H), 2.87 - 2.74 (m, 4H), 2.71 - 2.62 (m, 2H), 2.41 - 2.36 (m, 4H), 2.34 - 2.30 (m, 8H), 2.14 (s, 3H), 1.64 (br s, 2H), 1.19 - 0.59 (m, 9H); LCMS (Method G): Rt = 1.54 min, m/z = 688.7 $[M+H]^+$; HPLC (Method A): Rt = 4.57 min, 98.69%.

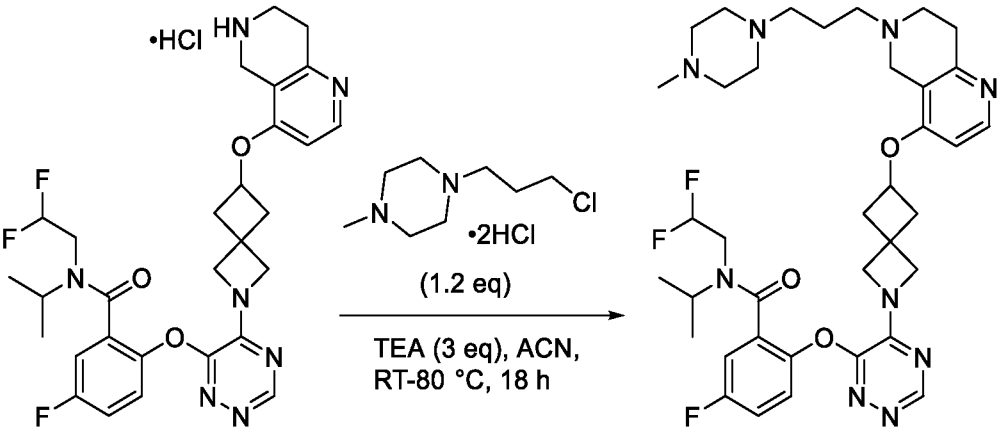
Example 121. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 147)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 1.2 equivalents of 1-(3-chloropropyl)pyrrolidine, except that 3 equivalents of TEA was used. The reaction was stirred at 80 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

Yield: 33.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.37 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 6.36 - 5.97 (m, 1H), 4.82 - 4.74 (m, 1H), 4.63 - 4.44 (m, 2H), 4.27 - 4.10 (m, 2H), 3.84 - 3.45 (m, 3H), 3.41 (s, 2H), 2.86 - 2.77 (m, 4H), 2.71 - 2.67 (m, 2H), 2.39 (br s, 9H), 1.66 (br s, 6H), 1.16 - 0.67 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.80 min, m/z = 695.3 $[M+H]^+$; HPLC (Method A): Rt = 5.45 min, 99.76%.

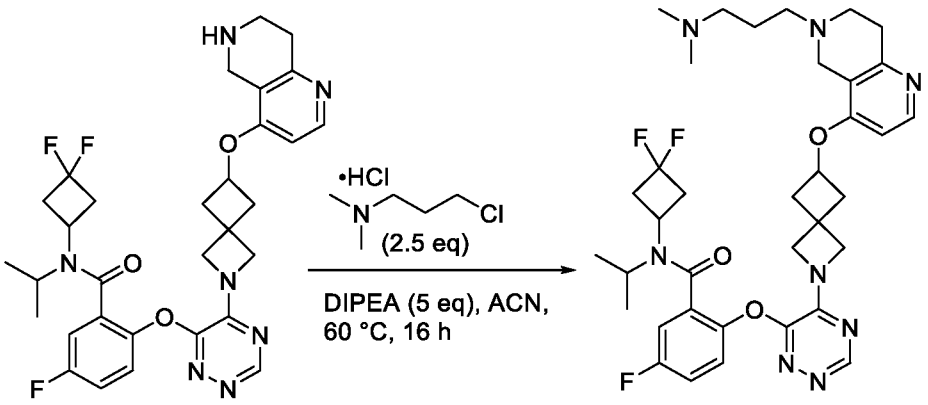
Example 122. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 152)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 1.2 equivalents of 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride, except that 3 equivalents of TEA was used. The reaction was stirred at 80 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(4-methylpiperazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

Yield: 29.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.52 - 7.37 (m, 3H), 6.69 (d, J = 5.8 Hz, 1H), 6.37 - 5.99 (m, 1H), 4.84 - 4.72 (m, 1H), 4.65 - 4.45 (m, 2H), 4.28 - 4.08 (m, 2H), 3.82 - 3.48 (m, 3H), 3.42 (s, 2H), 2.85 - 2.78 (m, 4H), 2.71 - 2.67 (m, 2H), 2.39 - 2.24 (m, 10H), 2.14 (s, 3H), 1.64 (br s, 2H), 1.18 - 0.68 (m, 6H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.60 min, m/z = 724.7 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 97.92%.

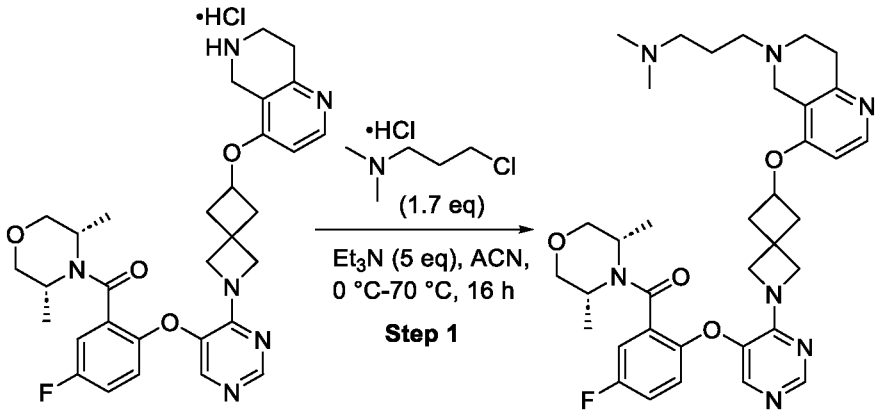
Example: 123. *N*-(3,3-Difluorocyclobutyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 187) – Procedure B



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 2.5 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C. The reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(3,3-difluorocyclobutyl)-2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 48.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.51 - 7.43 (m, 1H), 7.43 - 7.25 (m, 2H), 6.68 (br s, 1H), 4-77-4.79 (m, 1H), 4.69 - 4.48 (m, 2H), 4.35 - 4.08 (m, 2H), 4.02 - 3.78 (m, 1H), 3.77 - 3.49 (m, 2H), 3.42 (br s, 2H), 2.94 - 2.75 (m, 4H), 2.76 - 2.62 (m, 4H), 2.58 - 2.52 (m, 4H), 2.42 - 2.27 (m, 1H), 2.27 - 2.18 (m, 2H), 2.12 (s, 6H), 1.63 (br s, 2H), 1.09 (br s, 3H), 0.71 (br s, 3H); LCMS (Method D): Rt = 1.79 min, m/z = 695.5 $[M+H]^+$; HPLC (Method F): Rt = 5.54 min, 97.81%.

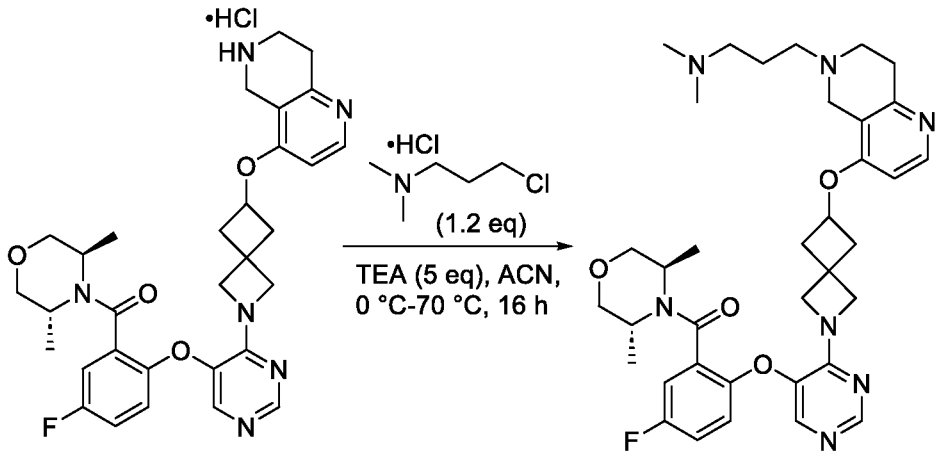
Example 124. (2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone (Compound No. 83)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone hydrochloride and 1.7 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride, except that 5 equivalents of TEA was used. The crude was purified by Prep HPLC (Method I) to afford (2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone.

Yield: 3.64%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.82 - 7.69 (m, 1H), 7.47 - 7.24 (m, 2H), 7.13 - 7.00 (m, 1H), 6.66 (d, *J* = 5.6 Hz, 1H), 4.80 - 4.69 (m, 1H), 4.45 - 4.04 (m, 5H), 3.81 - 3.54 (m, 3H), 3.41 (s, 2H), 2.84 - 2.74 (m, 4H), 2.70 - 2.66 (m, 4H), 2.35 - 2.31 (m, 2H), 2.30 - 2.17 (m, 4H), 2.12 (s, 6H), 1.62 (quin, *J* = 7.2 Hz, 2H), 1.44 - 1.17 (m, 6H); LCMS (Method G): Rt = 1.56 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.64 min, 99.57%; Chiral SFC (Method Z): Rt = 3.05 min, 100%.

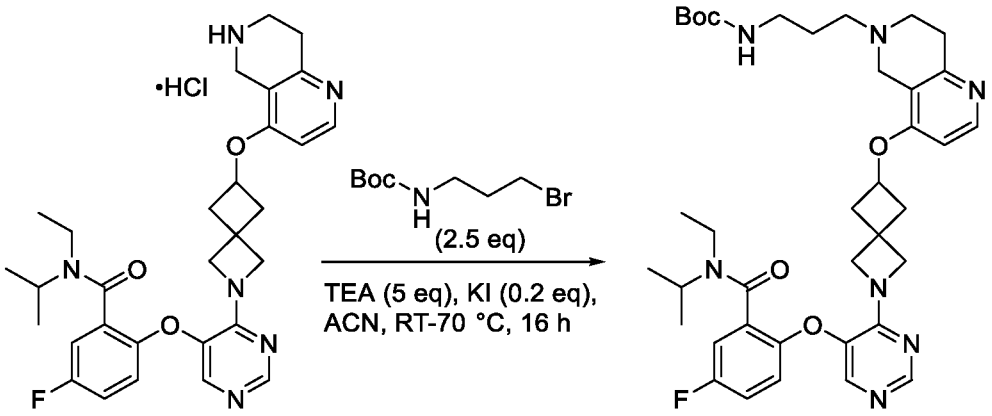
Example 125. (2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-Azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone (Compound No. 77)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone hydrochloride and 1.2 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride, except that 5 equivalents of TEA was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column(120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone.

Yield: 19.73%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, *J* = 5.7 Hz, 1H), 7.70 (s, 1H), 7.46 - 7.22 (m, 2H), 7.06 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.66 (d, *J* = 5.7 Hz, 1H), 4.74 (quin, *J* = 6.7 Hz, 1H), 4.32 - 4.09 (m, 4H), 3.99 - 3.59 (m, 5H), 3.41 (s, 2H), 2.87 - 2.75 (m, 4H), 2.71 - 2.64 (m, 2H), 2.62 - 2.54 (m, 2H), 2.31 - 2.17 (m, 5H), 2.12 (s, 6H), 1.62 (quin, *J* = 7.3 Hz, 2H), 1.37 - 1.02 (m, 6H); LCMS (Method B): Rt = 1.27 min, m/z = 660.2 $[M+H]^+$; HPLC (Method A): Rt = 4.62 min, 98.45%.

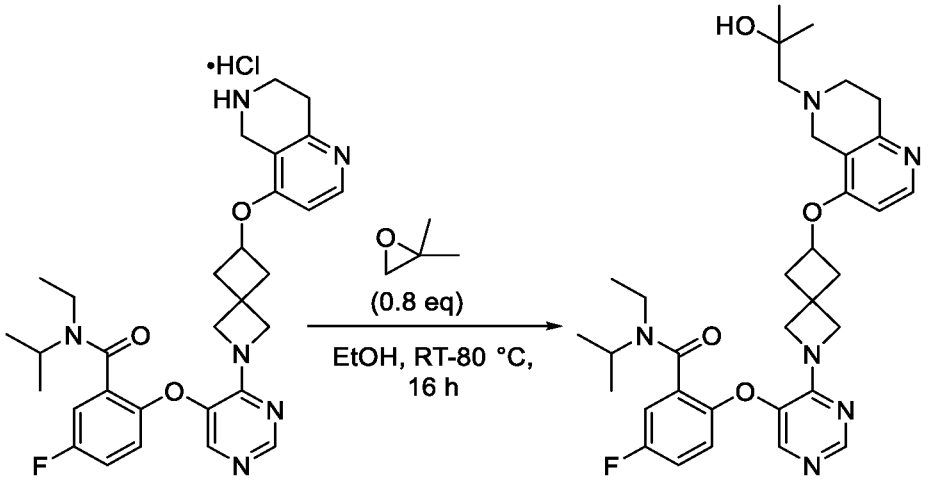
Example 126. *tert*-Butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate (Compound No. 119)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 2.5 equivalents of *tert*-butyl (3-bromopropyl)carbamate, except that 5 equivalents of TEA and 0.2 equivalent of KI were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate as a solid.

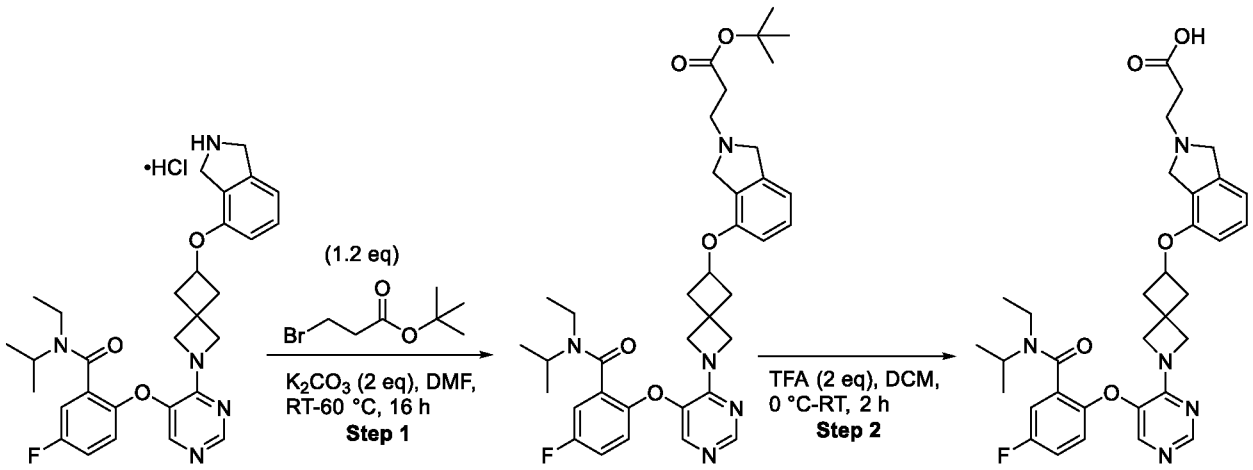
Yield: 53.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.4 Hz, 1H), 7.76 - 7.66 (s, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.85 - 6.75 (m, 1H), 6.67 (d, J = 5.4 Hz, 1H), 4.85 - 4.64 (m, 1H), 4.45 - 4.07 (m, 4H), 3.83 - 3.67 (m, 1H), 3.45 - 3.37 (m, 3H), 3.27 - 3.10 (m, 2H), 2.97 (q, J = 6.5 Hz, 2H), 2.85 - 2.74 (m, 4H), 2.67 - 2.61 (m, 2H), 2.30 - 2.21 (m, 2H), 1.69 - 1.55 (m, 2H), 1.37 (s, 9H), 1.25 - 0.96 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.88 min, m/z = 704.7 $[M+H]^+$; HPLC (Method A): Rt = 5.84 min, 99.32%.

Example 127. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-2-methylpropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 64)

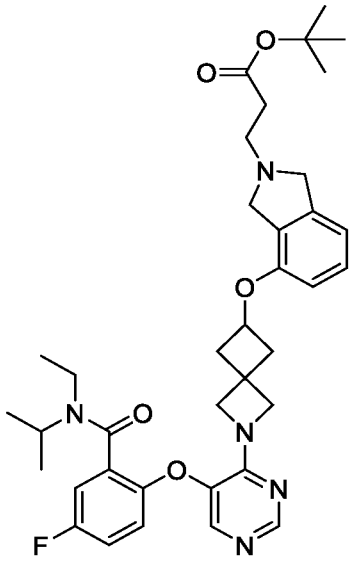


To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (200 mg, 0.366 mmol) in ethanol (5 mL), 2,2-dimethyloxirane (21.11 mg, 0.293 mmol) was added at RT. The reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain product (LCMS purity: 86%). The isolated product was impure. Therefore, the compound was re-purified by Prep HPLC (Method AF) to afford *N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-2-methylpropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (46.32 mg, 20.14% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.20 - 8.14 (m, 1H), 7.77 - 7.65 (m, 1H), 7.35 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.62 (m, 1H), 4.77 - 4.70 (m, 1H), 4.29 - 4.08 (m, 5H), 3.79 - 3.72 (m, 1H), 3.58 (s, 2H), 3.45 - 3.35 (m, 1H), 3.27 - 3.09 (m, 1H), 2.91 - 2.72 (m, 6H), 2.40 (s, 2H), 2.30 - 2.16 (m, 2H), 1.27 - 0.93 (m, 15H); LCMS (Method D): Rt = 2.10 min, m/z = 619.4 $[M+H]^+$; HPLC (Method A): Rt = 5.24 min, 99.94%.

Example 128. 3-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoic acid (Compound No. 33)



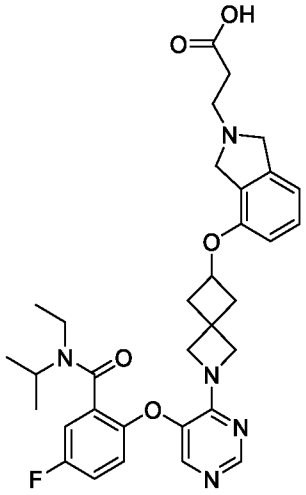
Step 1. tert-Butyl 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoate



In a pressure vial, *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (250 mg, 0.470 mmol) and *tert*-butyl 3-bromopropanoate (118 mg, 0.564 mmol) was added in DMF (5 mL) under a nitrogen atmosphere. K_2CO_3 (130 mg, 0.940 mmol) was added to this reaction mixture at RT, and the reaction was stirred at 60 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, diluted with ice-cold water (10 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with saturated ammonium chloride solution (20 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to afford *tert*-butyl 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoate

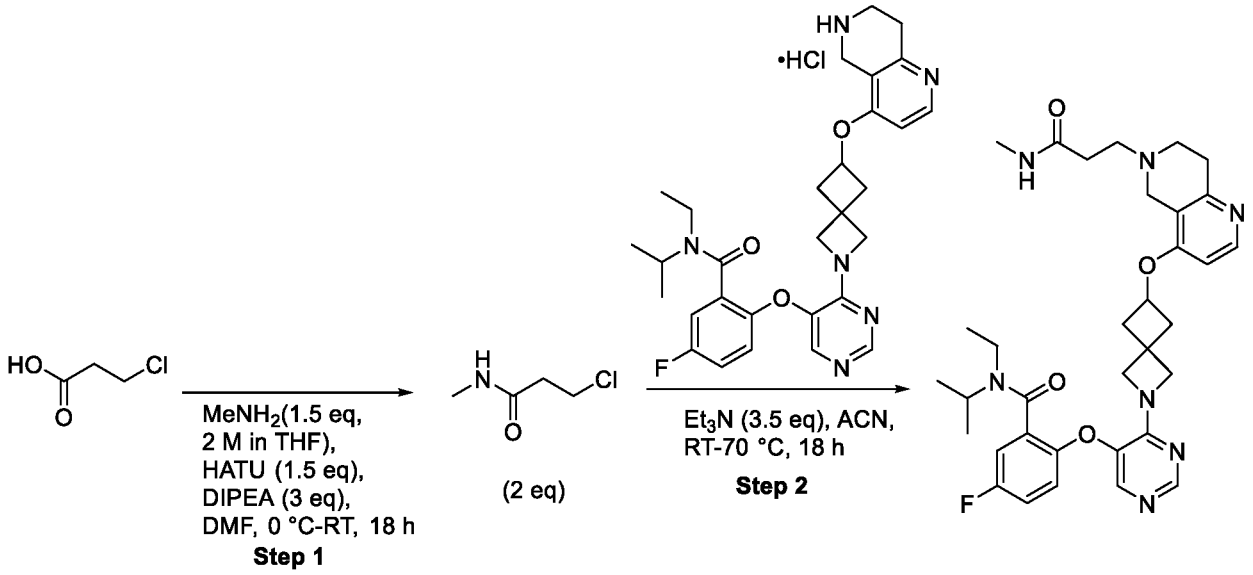
(130 mg, 37.8% yield) as a solid. LCMS (Method B): Rt = 2.13 min, m/z = 660.3 $[M+H]^+$; 90.31%.

Step 2. 3-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoic acid

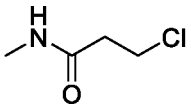


In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoate (100 mg, 0.152 mmol) was added in DCM (5 mL). To this solution, TFA (34.6 mg, 0.303 mmol) was added dropwise at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method Y) to obtain 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)propanoic acid (19.98 mg, 21.59% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.10 - 7.00 (m, 1H), 6.81 (d, J = 7.4 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 4.70 - 4.62 (m, 1H), 4.47 - 4.08 (m, 4H), 3.86 (s, 2H), 3.81 - 3.78 (m, 2H), 3.78 - 3.70 (m, 1H), 3.44 - 3.39 (m, 1H), 3.25 - 3.21 (m, 1H), 2.90 (t, J = 7.1 Hz, 2H), 2.80 -2.71 (m, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.28 - 2.19 (m, 2H), 1.22 - 0.98 (m, 9H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.39 min, m/z = 604.3 $[M+H]^+$; HPLC (Method A): Rt = 6.64 min, 99.73%.

Example 129. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 115)

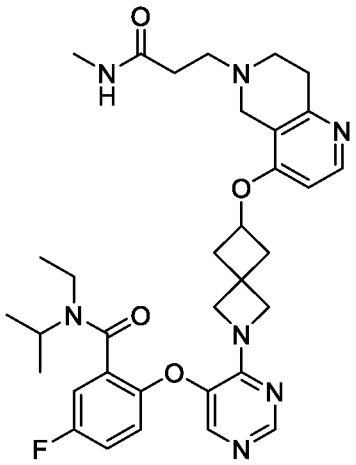


Step 1. 3-Chloro-N-methylpropanamide



To a solution of 3-chloropropanoic acid (1 g, 9.21 mmol) and methylamine (6.91 mL, 13.82 mmol, 2M in THF) in ACN (5 mL), DIPEA (4.83 mL, 27.6 mmol) and HATU (5.26 g, 13.82 mmol) were added at 0 °C. The reaction was stirred RT for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80% EtOAc in hexane) to obtain pure 3-chloro-*N*-methylpropanamide (800 mg, 71.4% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (br s, 1H), 3.78 (t, J = 6.4 Hz, 2H), 2.59 (d, J = 4.6 Hz, 3H), 2.54 (t, J = 6.4 Hz, 2H).

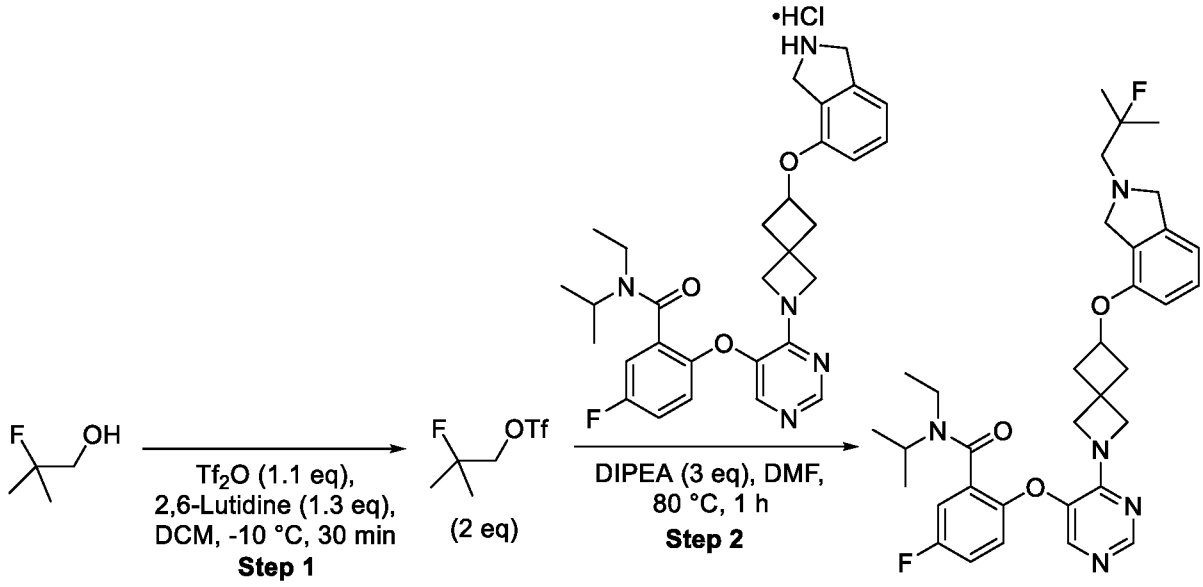
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(methylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



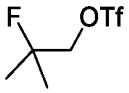
This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 2 equivalents of 3-chloro-*N*-methylpropanamide, except that 3.5 equivalents of TEA was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH), then by Prep HPLC (Method B) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 6.68%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.85 - 7.80 (m, 1H), 7.77 - 7.67 (m, 1H), 7.33 - 7.22 (m, 2H), 7.09 - 7.00 (m, 1H), 6.69 - 6.65 (m, 1H), 4.78 - 4.70 (m, 1H), 4.48 - 4.08 (m, 4H), 3.82 - 3.70 (m, 1H), 3.43 (s, 2H), 3.42 - 3.34 (m, 1H), 3.28 - 3.11 (m, 2H), 2.83 - 2.68 (m, 7H), 2.57 (d, *J* = 4.6 Hz, 3H), 2.33 - 2.22 (m, 4H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.50 min, m/z = 632.6 $[M+H]^+$; HPLC (Method A): Rt = 4.72 min, 97.82%.

Example 130. ***N-ethyl-5-fluoro-2-((4-(6-((2-(2-fluoro-2-methylpropyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide*** (Compound No. 41)

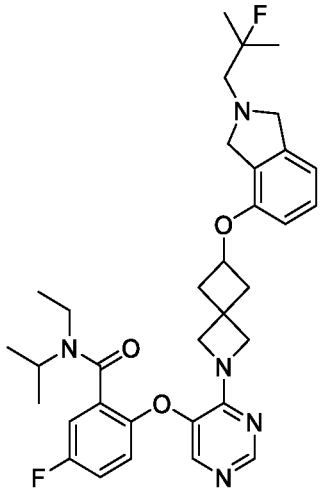


Step 1. 2-Fluoro-2-methylpropyl trifluoromethanesulfonate



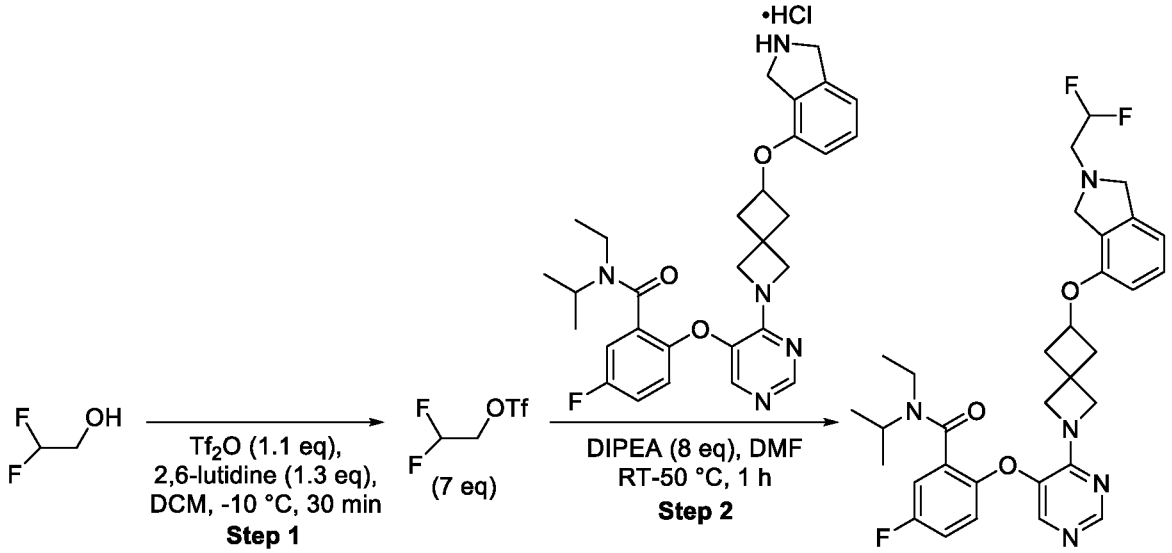
To a stirred solution of 2-fluoro-2-methylpropan-1-ol (0.521 mL, 5.43 mmol) in DCM (20 mL), 2,6-lutidine (0.822 mL, 7.06 mmol) was added at RT. To this reaction mixture, triflic anhydride (1.009 mL, 5.97 mmol) was added at -10 °C, and the reaction was stirred at the same temperature for 30 min. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was diluted with DCM (25 mL) and washed with aqueous 1.5 N HCl (25 mL) and then with aqueous $NaHCO_3$ solution (25 mL). The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 2-fluoro-2-methylpropyl trifluoromethanesulfonate (1.075 g, 88% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.82 (s, 1H), 4.77 (s, 1H), 1.43 (s, 3H), 1.37 (s, 3H). This material was used without further purification.

Step 2. N-ethyl-5-fluoro-2-((4-(6-((2-(2-fluoro-2-methylpropyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

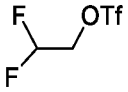


To a stirred solution of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride (200 mg, 0.352 mmol) and 2-fluoro-2-methylpropyl trifluoromethanesulfonate (158 mg, 0.704 mmol) in DMF (5 mL), DIPEA (0.184 mL, 1.056 mmol) was added. The reaction was stirred at 80 °C for 1 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with ice-cold water (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method AE) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((2-(2-fluoro-2-methylpropyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (11.09 mg, 4.99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.23 (m, 1H), 7.81 - 7.58 (m, 1H), 7.35 - 7.19 (m, 2H), 7.16 - 7.00 (m, 2H), 6.80 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.72 - 4.60 (m, 1H), 4.30 - 4.05 (m, 4H), 3.94 (s, 2H), 3.87 (s, 2H), 3.75 (sep, J = 6.6 Hz, 1H), 3.43 - 3.37 (m, 1H), 3.28 - 3.03 (m, 1H), 2.85 (s, 1H), 2.79 (s, 1H), 2.78 - 2.70 (m, 2H), 2.29 - 2.16 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.23 - 0.96 (m, 9H); LCMS (Method B): Rt = 1.83 min, m/z = 606.3 $[M+H]^+$; HPLC (Method A): Rt = 7.18 min, 96.41%.

Example 131. 2-((4-(6-((2-(2,2-Difluoroethyl)isoindolin-4-yl)oxy)-2-Azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 49)

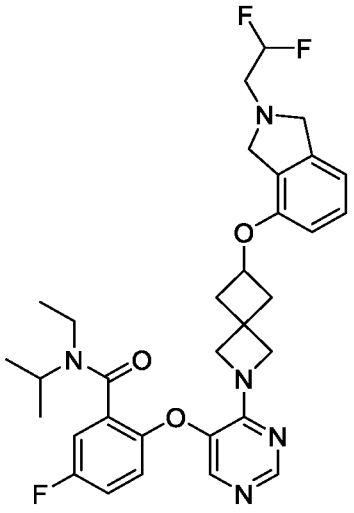


Step 1. 2,2-Difluoroethyl trifluoromethanesulfonate



This compound was synthesized following the procedure described for the synthesis of Example 130, step 1, starting with 1 equivalent of 2,2-difluoroethan-1-ol. After completion, the reaction was diluted with DCM and washed with aqueous 1.5 N HCl and then with aqueous $NaHCO_3$ solution. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 2,2-difluoroethyl trifluoromethanesulfonate as an oil. This material was used without further purification.

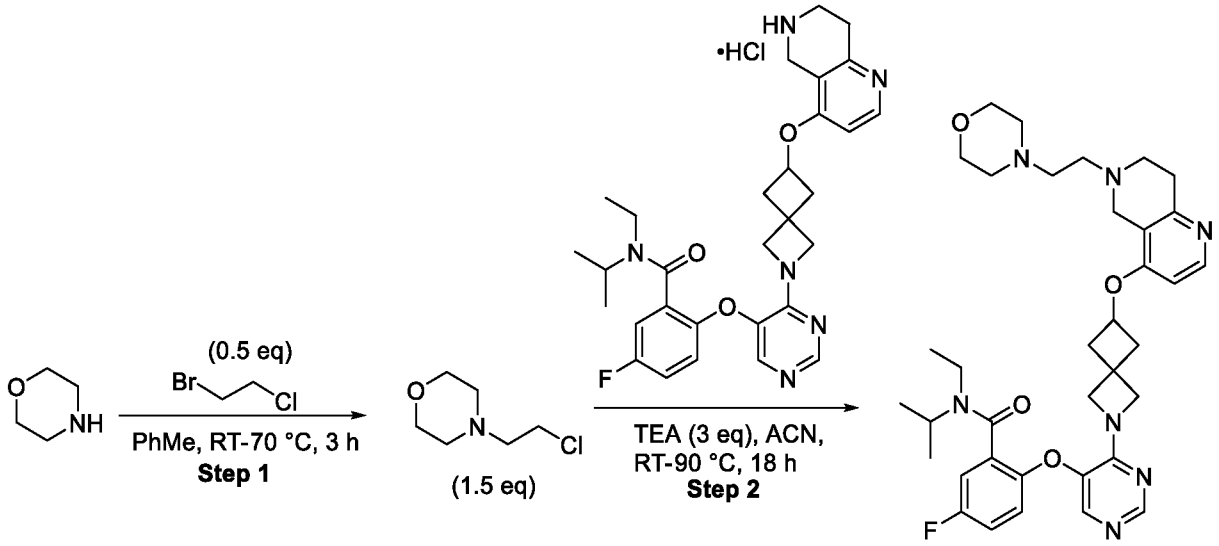
Step 2. *2-((4-(6-((2-(2,2-Difluoroethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide*



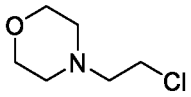
This compound was synthesized following the procedure described for the synthesis of Example 130, step 2, starting with *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride, except that 7 equivalents of 2,2-difluoroethyl trifluoromethanesulfonate and 8 equivalents of DIPEA were used. The reaction was stirred at 50 °C. After completion, the reaction was quenched with ice-cold water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method N) to obtain 2-((4-(6-((2-(2,2-difluoroethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 5.73%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.21 (m, 1H), 7.79 - 7.64 (m, 1H), 7.36 - 7.21 (m, 2H), 7.18 - 7.10 (m, 1H), 7.10 - 6.98 (m, 1H), 6.82 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.34 - 5.98 (m, 1H), 4.73 - 4.61 (m, 1H), 4.32 - 4.06 (m, 4H), 3.99 (s, 2H), 3.93 (s, 2H), 3.75 (spt, J = 6.6 Hz, 1H), 3.46 - 3.37 (m, 2H), 3.28 - 3.18 (m, 1H), 3.11 (dt, J = 4.2, 16.0 Hz, 2H), 2.80 - 2.70 (m, 2H), 2.28 - 2.16 (m, 2H), 1.34 - 0.91 (m, 9H), one proton merged with solvent peaks; LCMS (Method D): Rt = 2.24 min, m/z = 596.4 $[M+H]^+$; HPLC (Method A): Rt = 6.64 min, 98.82%.

Example 132. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-morpholinoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 73)

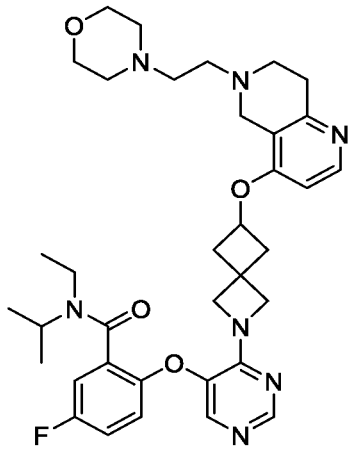


Step 1. 4-(2-Chloroethyl)morpholine



To a stirred solution of morpholine (1.0 g, 11.48 mmol) in toluene (4 mL), 1-bromo-2-chloroethane (0.823 g, 5.74 mmol) was added at RT under a nitrogen atmosphere, and the reaction was stirred at 70 °C for 3 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 40% EtOAc in hexane) to obtain 4-(2-chloroethyl)morpholine (350 mg, 18.73% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (t, J = 6.8 Hz, 2H), 3.61 - 3.51 (m, 4H), 2.63 (t, J = 6.8 Hz, 2H), 2.47 - 2.39 (m, 4H); LCMS (Method D): Rt = 1.11 min, m/z = 150.0 $[M+H]^+$; 91.91%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-morpholinoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



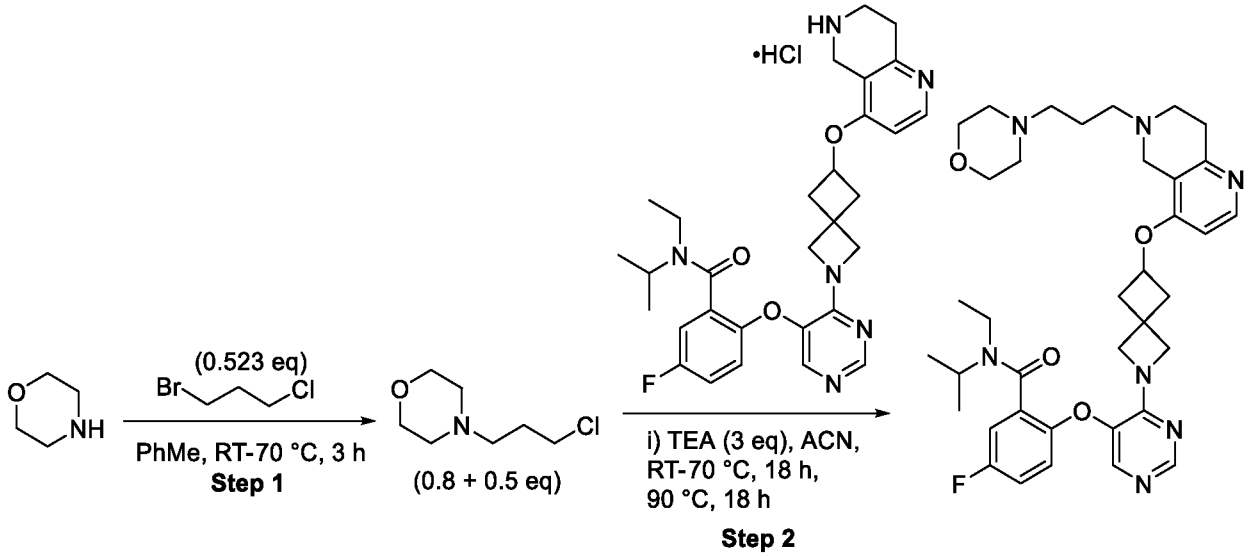
Step 2 was performed following the same procedure in two batches, 120 mg and 200 mg batches.

This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.5 equivalents of 4-(2-chloroethyl)morpholine, except that 3 equivalents of TEA was used. The reaction was stirred in a pressure vial at 90 °C. The reaction mixtures from both batches were combined, diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN)

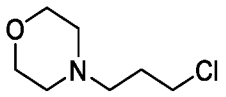
to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-morpholinoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 26.42% (combined yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.47 - 4.08 (m, 5H), 3.80 - 3.68 (m, 1H), 3.56 (t, J = 4.5 Hz, 4H), 3.48 (s, 2H), 3.44 - 3.37 (m, 1H), 3.27 - 3.11 (m, 2H), 2.82 - 2.71 (m, 6H), 2.66 - 2.60 (m, 2H), 2.41 (br s, 4H), 2.30 - 2.21 (m, 2H), 1.23 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.67 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.85 min, 99.84%.

Example 133. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-morpholinopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 72)

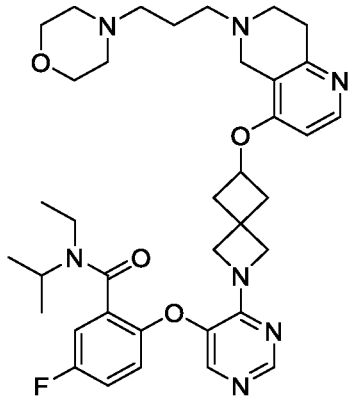


Step 1. 4-(3-Chloropropyl)morpholine



This compound was synthesized following the procedure described for the synthesis of Example 132, step 1, starting with morpholine, except that 0.523 equivalent of 1-bromo-3-chloropropane was used. After completion, the reaction was concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 50% EtOAc in hexane) to obtain 4-(3-chloropropyl)morpholine (300 mg, 30.4% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 - 3.70 (m, 4H), 3.63 (t, J = 6.5 Hz, 2H), 2.65 - 2.36 (m, 6H), 1.99 (p, J = 6.8 Hz, 2H); LCMS (Method D): Rt = 1.28 min, m/z = 164.2 $[M+H]^+$; 96.15%.

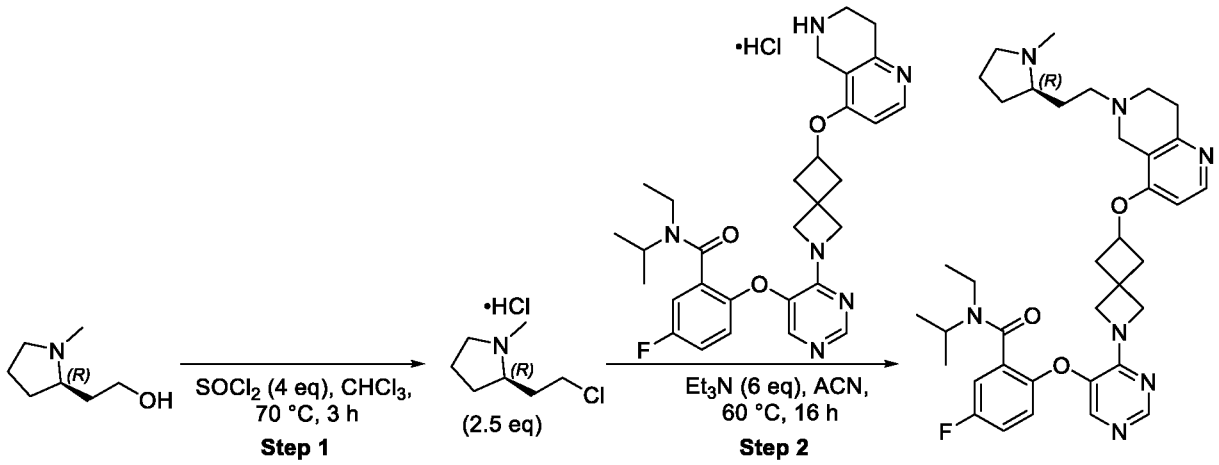
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-morpholinopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



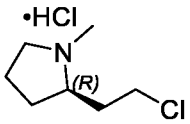
To a stirred solution of *N*-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (180 mg, 0.309 mmol) and 4-(3-chloropropyl)morpholine (40.4 mg, 0.247 mmol) in acetonitrile (5 mL), TEA (0.129 ml, 0.926 mmol) was added at RT under a nitrogen atmosphere. The reaction was stirred at 70 °C for 18 h. The starting material was not consumed. Therefore, the reaction was cooled to RT and another lot of 4-(3-chloropropyl)morpholine (25.3 mg, 0.154 mmol) was added. The reaction was stirred at 90 °C for another 18 h under a nitrogen atmosphere. After completion, the reaction was concentrated under reduced pressure, diluted with water (10 mL), and extracted with 10% MeOH in DCM (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-morpholinopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 10.27%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.81 - 4.69 (m, 1H), 4.46 - 4.07 (m, 5H), 3.82 - 3.69 (m, 1H), 3.57 (t, *J* = 4.5 Hz, 4H), 3.41 (s, 2H), 3.40 - 3.37 (m, 1H), 3.27 - 3.12 (m, 2H), 2.83 - 2.79 (m, 4H), 2.68 - 2.65 (m, 2H), 2.32 - 2.20 (m, 5H), 1.66 (quin, *J* = 7.2 Hz, 2H), 1.23 - 0.98 (m, 9H), three protons merged with solvent peaks. LCMS (Method D): Rt = 1.63 min, m/z = 674.6 $[M+H]^+$; HPLC (Method A): Rt = 4.97 min, 95.82%.

Example 134. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 103)

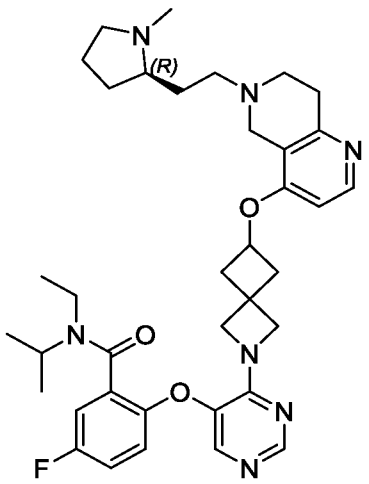


Step 1. (R)-2-(2-Chloroethyl)-1-methylpyrrolidine hydrochloride



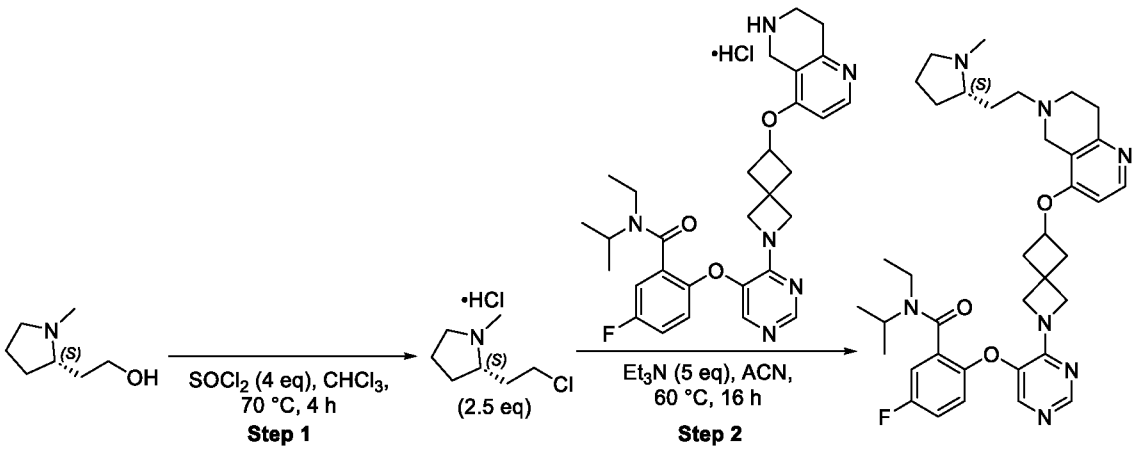
To a stirred solution of (*R*)-2-(1-methylpyrrolidin-2-yl)ethan-1-ol (0.2 g, 1.548 mmol) in chloroform (5 mL), thionyl chloride (0.452 mL, 6.19 mmol) was added slowly at RT. The reaction was stirred at 70 °C for 3 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to RT and concentrated under reduced pressure. The residue was triturated with hexane (3 x 20 mL), and the supernatant was decanted. The solid was dried under reduced pressure to obtain crude (*R*)-2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (0.265 g, 93% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 10.82 (br s, 1H), 3.90 - 3.79 (m, 1H), 3.72 - 3.64 (m, 1H), 3.58 - 3.48 (m, 1H), 3.41 - 3.36 (m, 1H), 3.10 - 2.96 (m, 1H), 2.78 (d, *J* = 5.0 Hz, 3H), 2.42 - 2.29 (m, 1H), 2.29 - 2.18 (m, 1H), 2.16 - 2.06 (m, 1H), 2.05 - 1.84 (m, 2H), 1.75 - 1.63 (m, 1H). This material was used without further purification.

Step 2. (R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

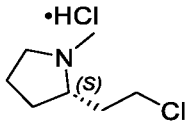


To a solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.15 g, 0.257 mmol) in acetonitrile (6 mL), TEA (0.215 mL, 1.543 mmol) was added at RT. To this reaction mixture, (*R*)-2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (0.118 g, 0.643 mmol) was added, and the reaction was stirred at 60 °C for 48 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.07 g, 40.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.19 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.78 - 4.70 (m, 1H), 4.47 - 4.02 (m, 4H), 3.80 - 3.69 (m, 1H), 3.52 - 3.34 (m, 2H), 3.28 - 3.11 (m, 2H), 2.97 - 2.89 (m, 1H), 2.83 - 2.73 (m, 4H), 2.70 - 2.66 (m, 2H), 2.31 - 2.22 (m, 2H), 2.21 (s, 3H), 2.07 - 1.98 (m, 2H), 1.92 - 1.81 (m, 2H), 1.66 - 1.56 (m, 2H), 1.26 - 1.32 (m, 2H), 1.22 - 0.96 (m, 9H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.65 min, m/z = 658.4 $[M+H]^+$; HPLC (Method A): Rt = 4.88 min, 98.38%; Chiral SFC (Method B): Rt = 1.27 min, 97.84%.

Example 135. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 102)



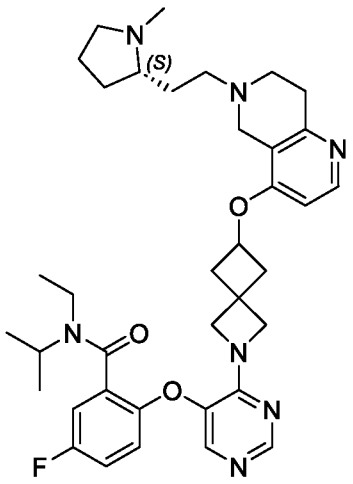
Step 1. (S)-2-(2-Chloroethyl)-1-methylpyrrolidine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 134, step 1, starting with 1 equivalent of (*S*)-2-(1-methylpyrrolidin-2-yl)ethan-1-ol. The residue was triturated with hexane, and the supernatant was decanted. The solid was dried under vacuum to obtain crude (*S*)-2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride as a semi-solid.

Yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (br s, 1H), 3.88 - 3.80 (m, 1H), 3.73 - 3.64 (m, 1H), 3.58 - 3.48 (m, 1H), 3.41 - 3.29 (m, 1H), 3.09 - 2.98 (m, 1H), 2.78 (d, J = 5.0 Hz, 3H), 2.42 - 2.32 (m, 1H), 2.29 - 2.19 (m, 1H), 2.17 - 2.06 (m, 1H), 2.05 - 1.85 (m, 2H), 1.76 - 1.64 (m, 1H). This material was used without further purification.

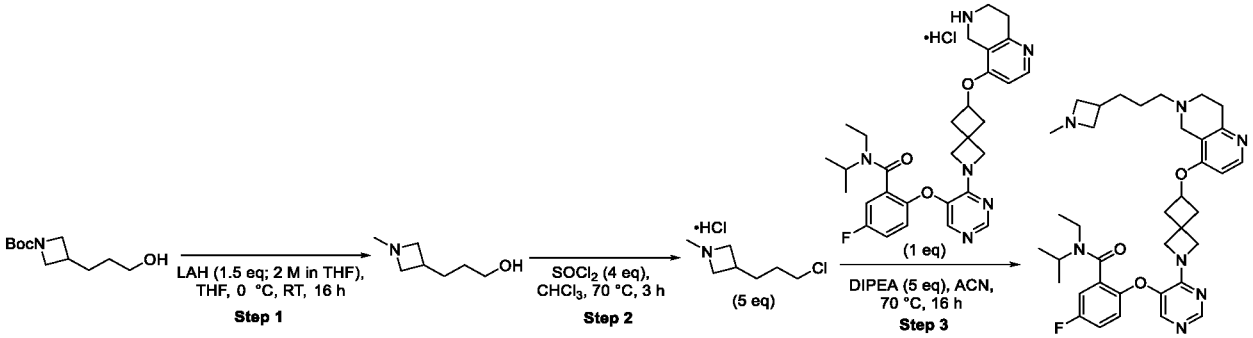
Step 2. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



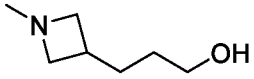
This compound was synthesized following the procedure described for the synthesis of Example 134, step 2, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 2.5 equivalents of (*S*)-2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride 5 equivalents and Et_3N were used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylpyrrolidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 29.94%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.06 (m, 4H), 3.81 - 3.69 (m, 1H), 3.48 - 3.36 (m, 2H), 3.27 - 3.12 (m, 2H), 2.97 - 2.89 (m, 1H), 2.84 - 2.74 (m, 4H), 2.71 - 2.67 (m, 2H), 2.30 - 2.23 (m, 2H), 2.21 (s, 3H), 2.08 - 1.99 (m, 2H), 1.93 - 1.80 (m, 2H), 1.66 - 1.56 (m, 2H), 1.45 - 1.33 (m, 2H), 1.23 - 0.97 (m, 9H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.84 min, m/z = 658.4 $[M+H]^+$; HPLC (Method A): Rt = 5.17 min, 98.57%; Chiral SFC (Method B): Rt = 1.27 min, 96.48%.

Example 136. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(1-methylazetidin-3-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 269)



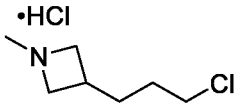
Step 1. 3-(1-Methylazetidin-3-yl)propan-1-ol



To a stirred solution of *tert*-butyl 3-(3-hydroxypropyl)azetidine-1-carboxylate (1.5 g, 6.97 mmol) in THF (25 mL) under a nitrogen atmosphere, LAH (5.23 mL, 10.45 mmol, 2M in THF) was added slowly at 0 °C. The reaction was stirred at RT for 16 h. After completion,

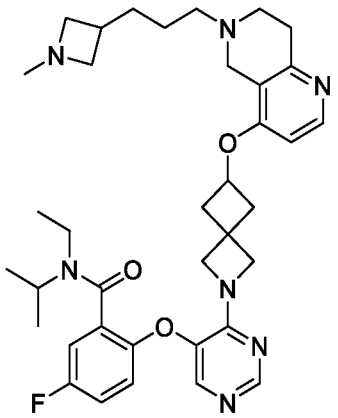
the reaction was cooled to 0 °C, and quenched with water (5 mL) and 10% aq. NaOH (5 mL). The mixture was stirred for 30 min, then was filtered through a Celite® pad, and the pad was washed with EtOAc (2 x 30 mL). The filtrate was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 3-(1-methylazetidin-3-yl)propan-1-ol (0.685 g, 76% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.34 (t, J = 5.1 Hz, 1H), 3.37 - 3.34 (m, 2H), 3.30 - 3.24 (m, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.34 - 2.19 (m, 1H), 2.15 (s, 3H), 1.50-1.44 (m, 2H), 1.38 - 1.27 (m, 2H). This material was used without further purification.

Step 2. 3-(3-Chloropropyl)-1-methylazetidine hydrochloride



To a stirred solution of 3-(1-methylazetidin-3-yl)propan-1-ol (0.535 g, 4.14 mmol) in $CHCl_3$ (5 mL), thionyl chloride (1.201 mL, 16.56 mmol) was added at 0 °C. The reaction was slowly warmed to RT and then stirred at 70 °C for 3 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was cooled to RT and concentrated under reduced pressure to obtain 3-(3-chloropropyl)-1-methylazetidine hydrochloride (0.78 g, quantitative yield) as a semi-solid. LCMS-ELSD (Method G): Rt = 0.45, m/z = 148.2 $[M+H]^+$; 34.1%. This material was used without further purification.

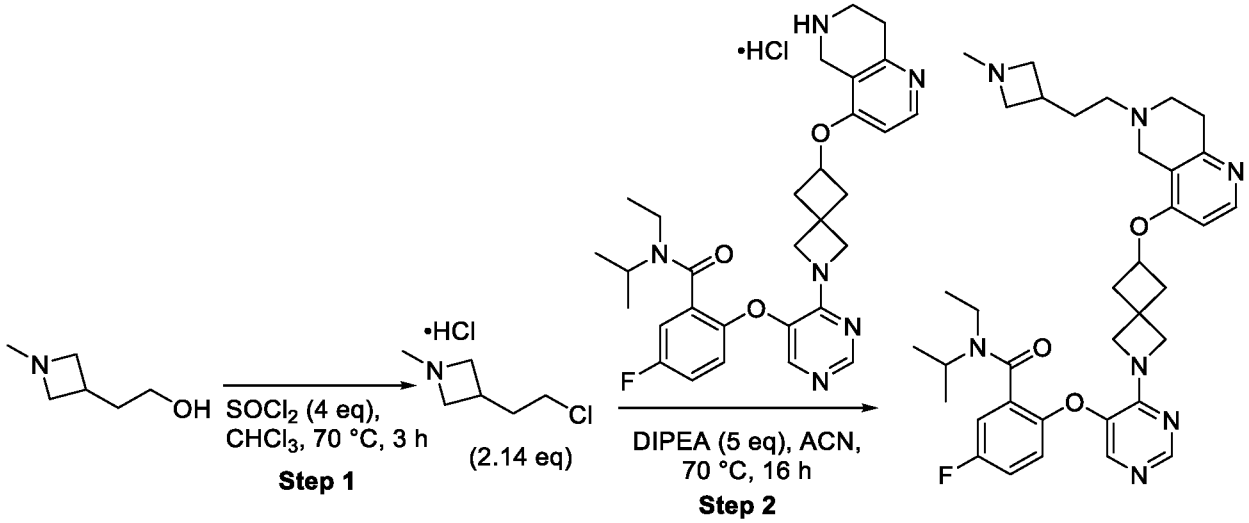
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(1-methylazetidin-3-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



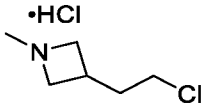
To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.3 g, 0.514 mmol) in ACN (10 mL), DIPEA (0.449 mL, 2.57 mmol) was added at RT. To this reaction mixture, 3-(3-chloropropyl)-1-methylazetidine hydrochloride

(0.474 g, 2.57 mmol) was added, and the reaction was stirred at 70 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(1-methylazetidin-3-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.025 g, 7.39% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.30 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.68 - 6.64 (m, 1H), 4.78 - 4.70 (m, 1H), 4.46 - 4.06 (m, 4H), 3.80 - 3.71 (m, 1H), 3.47 - 3.35 (m, 2H), 3.28 - 3.13 (m, 2H), 2.83 - 2.74 (m, 5H), 2.71 - 2.60 (m, 4H), 2.32 - 2.22 (m, 4H), 2.11 (s, 3H), 1.88 - 1.76 (m, 2H), 1.69 - 1.42 (m, 4H), 1.14 - 0.78 (m, 9H); LCMS (Method G): Rt = 1.77 min, m/z = 658.7 $[M+H]^+$; HPLC (Method A): Rt = 5.06 min, 99.59%.

Example 137. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 273)



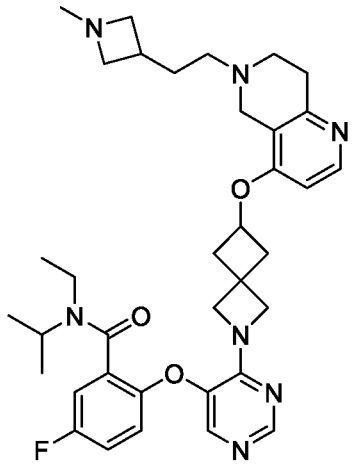
Step 1. 3-(2-Chloroethyl)-1-methylazetidine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 136, step 2, starting with 1 equivalent of 2-(1-methylazetidin-3-yl)ethan-1-ol, to obtain crude 3-(2-chloroethyl)-1-methylazetidine hydrochloride. This material was used without further purification.

Yield: 97%; LCMS-ELSD (Method G): Rt = 0.39 min, m/z = 134.1 $[M+H]^+$; 100%.

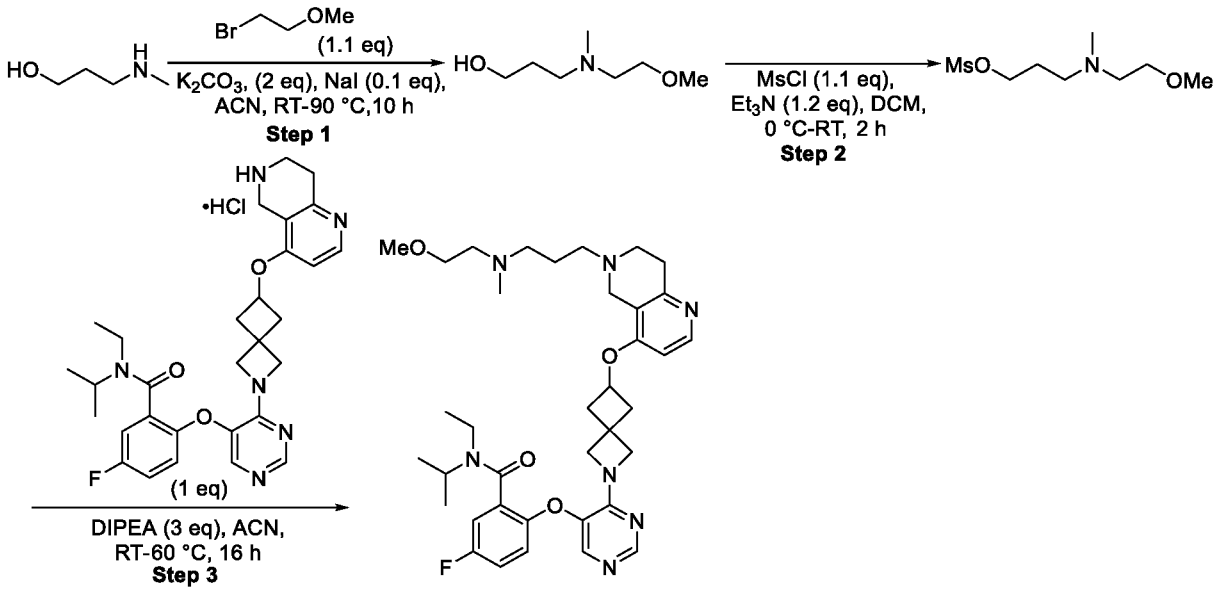
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



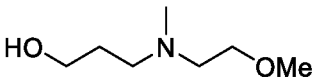
This compound was synthesized following the procedure described for the synthesis of Example 136, step 3, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 2.14 equivalents of 3-(2-chloroethyl)-1-methylazetidine hydrochloride was used. The crude was purified by Prep HPLC (Method C) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 7.74%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.78 - 4.69 (m, 1H), 4.47 - 4.07 (m, 4H), 3.80 - 3.71 (m, 1H), 3.47 - 3.39 (m, 2H), 3.27 - 3.11 (m, 2H), 2.82 - 2.73 (m, 5H), 2.73 - 2.62 (m, 2H), 2.46 - 2.38 (m, 6H), 2.30 - 2.24 (m, 2H), 2.21 (s, 3H), 1.93 - 1.83 (m, 1H), 1.45 - 1.36 (m, 1H), 1.14 - 0.98 (m, 9H); LCMS (Method B): Rt = 1.05 min, m/z = 644.4 $[M+H]^+$; HPLC (Method A): Rt = 4.82 min, 99.38%.

Example 138. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((2-methoxyethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 74)

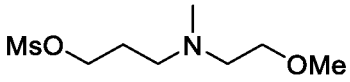


Step 1. 3-((2-Methoxyethyl)(methyl)amino)propan-1-ol



To a stirred solution of 3-(methylamino)propan-1-ol (5 g, 56.1 mmol) dissolved in ACN (50 mL), K_2CO_3 (15.50 g, 112 mmol) was added at RT under a nitrogen atmosphere. 1-Bromo-2-methoxyethane (8.58 g, 61.7 mmol) and sodium iodide (0.841 g, 5.61 mmol) were added to this reaction mixture at RT. The reaction was heated to 90 °C for 10 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to RT, and the solvent was evaporated. The residue was quenched with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 3-((2-methoxyethyl)(methyl)amino)propan-1-ol (4.6 g, 48.7% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.42 (br s, 1H), 3.41-3.37 (m, 4H), 3.23 (s, 3H), 2.45 (t, J = 6.0 Hz, 2H), 2.36 (t, J = 6.8 Hz, 2H), 2.15 (s, 3H), 1.58 - 1.49 (m, 2H); LCMS (Method D): Rt = 0.95 min, m/z = 148.3 $[M+H]^+$, 87.35%. This material was used without further purification.

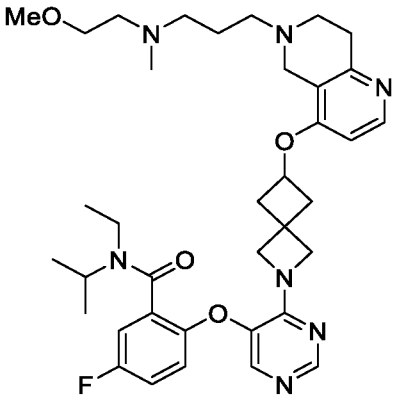
Step 2. 3-((2-Methoxyethyl)(methyl)amino)propyl methanesulfonate



To a stirred solution of 3-((2-methoxyethyl)(methyl)amino)propan-1-ol (0.2 g, 1.359 mmol) in DCM (10 mL), TEA (0.227 mL, 1.630 mmol) was added at 0 °C under a nitrogen atmosphere. To this reaction mixture, methanesulfonyl chloride (0.116 mL, 1.494 mmol) was added, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored

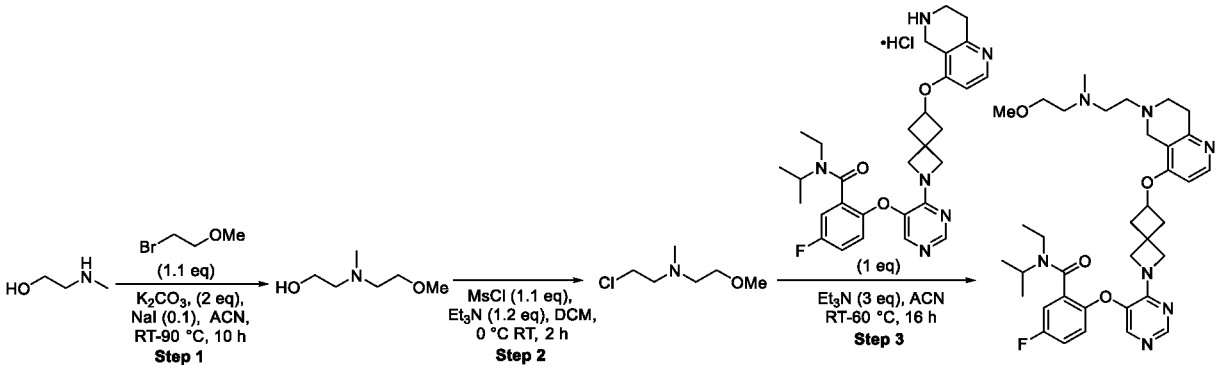
by TLC (100% EtOAc). After completion, the reaction was quenched with water (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 3-((2-methoxyethyl)(methyl)amino)propyl methanesulfonate (0.12 g, 37.6 %) as a semi-solid. LCMS-ELSD (Method B): Rt = 0.35 min, m/z = 226.3 $[M+H]^+$, 96.04%. This material was used without further purification.

Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((2-methoxyethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

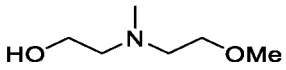


To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.1 g, 0.171 mmol) in ACN (4 mL), DIPEA (0.071 g, 0.549 mmol) was added at RT. To this reaction mixture, 3-((2-methoxyethyl)(methyl)amino)propyl methanesulfonate (0.038 g, 0.171 mmol) was added, and the reaction was stirred at 60 °C for 16 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by Prep HPLC (Method AH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((2-methoxyethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (19.12 mg, 15.33% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.51 - 3.97 (m, 4H), 3.81 - 3.68 (m, 1H), 3.50 - 3.36 (m, 5H), 3.22 (s, 3H), 2.84 - 2.73 (m, 4H), 2.71 - 2.63 (m, 2H), 2.49 - 2.42 (m, 5H), 2.40 - 2.32 (m, 2H), 2.30 - 2.19 (m, 2H), 2.17 (s, 3H), 1.68 - 1.57 (m, 2H), 1.22 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.72 min, m/z = 676.4 $[M+H]^+$; HPLC (Method A): Rt = 5.13 min, 99.14%.

Example 139. ***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-((2-methoxyethyl)(methyl)amino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 84)



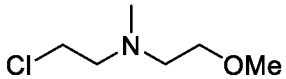
Step 1. 2-((2-Methoxyethyl)(methyl)amino)ethan-1-ol



This compound was synthesized following the procedure described for the synthesis of Example 138, step 1, starting with 1-bromo-2-methoxyethane, except that 1 equivalent of 2-(methylamino)ethan-1-ol was used. After completion, the reaction was cooled to RT, and the solvent was evaporated under reduced pressure. The residue was quenched with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 2-((2-methoxyethyl)(methyl)amino)ethan-1-ol as a semi-solid.

Yield: 50.8%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, J = 7.1 Hz, 2H), 3.50 (t, J = 5.6 Hz, 2H), 3.37 (s, 3H), 2.66 (t, J = 7.1 Hz, 2H), 2.61 (t, J = 5.6 Hz, 2H), 2.35 (s, 3H), one proton was merged with solvent peaks. This material was used without further purification.

Step 2. 2-Chloro-N-(2-methoxyethyl)-N-methylethan-1-amine

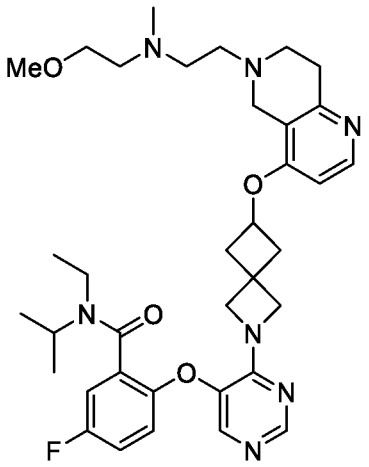


This compound was synthesized following the procedure described for the synthesis of Example 138, step 2, starting with 2-((2-methoxyethyl)(methyl)amino)ethan-1-ol. After completion, the reaction was quenched with 2N NaOH and extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude 2-chloro-*N*-(2-methoxyethyl)-*N*-methylethan-1-amine as a semi-solid.

Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, J = 7.1 Hz, 2H), 3.51 (t, J = 5.6 Hz, 2H), 3.38 (s, 3H), 2.83 (t, J = 7.1 Hz, 2H), 2.69 (t, J = 5.6 Hz, 2H), 2.38 (s, 3H); LCMS-ELSD

(Method B): Rt = 0.31 min, m/z = 152.3 $[M+H]^+$, 99.82%. This material was used without further purification.

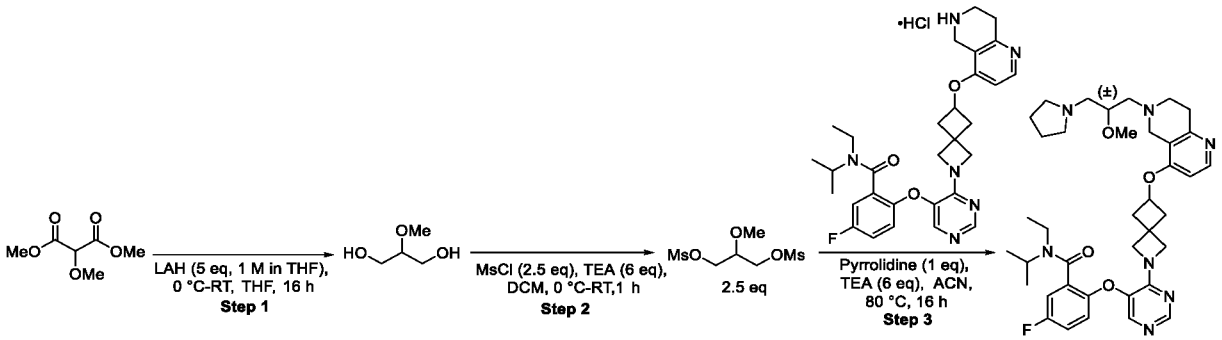
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-((2-methoxyethyl)(methyl)amino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



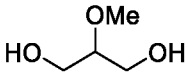
This compound was synthesized following the procedure described for the synthesis of Example 138, step 3, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1 equivalent of 2-chloro-*N*-(2-methoxyethyl)-*N*-methylethan-1-amine was used. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by Prep HPLC (Method M) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-((2-methoxyethyl)(methyl)amino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 8.49%; ^{1}H NMR (400 MHz, DMSO): δ 8.32 - 8.25 (m, 1H), 8.22 - 8.15 (m, 1H), 7.78 - 7.66 (m, 1H), 7.36 - 7.19 (m, 2H), 7.12 - 6.99 (m, 1H), 6.68 - 6.62 (m, 1H), 4.81 - 4.61 (m, 1H), 4.47 - 4.05 (m, 4H), 3.79 - 3.70 (m, 1H), 3.46 (br s, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 3.37 - 3.30 (m, 2H), 3.23 (s, 3H), 2.85 - 2.69 (m, 7H), 2.64 - 2.53 (m, 5H), 2.33 - 2.22 (m, 2H), 2.21 (s, 3H), 1.26 - 0.93 (m, 9H); LCMS (Method B): Rt = 1.45 min, m/z = 662.5 $[M+H]^+$, 99.13%; HPLC (Method A): Rt = 5.16 min, 96.29%.

Example 140. (±)-***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 207)

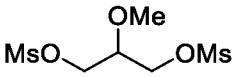


Step 1. 2-Methoxypropane-1,3-diol



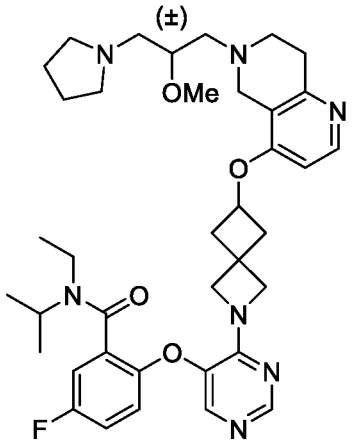
To a stirred solution of dimethyl 2-methoxymalonate (820 mg, 5.06 mmol) in THF (15 mL) under a nitrogen atmosphere, $LiAlH_4$ (25.3 mL, 25.3 mmol, 1 M in THF) was added at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, and quenched with cold water (5 mL) and 10% aq. NaOH (5 mL). The reaction was stirred for 30 min, filtered through a Celite® pad, and the pad was washed with EtOAc (3 x 25 mL). The filtrate was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain 2-methoxypropane-1,3-diol (190 mg, 35.46% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84-3.81 (m, 2H), 3.74-3.70 (m, 2H), 3.50 (s, 3H), 3.42 - 3.37 (m, 1H), -OH protons were not observed.

Step 2. 2-Methoxypropane-1,3-diyl dimethanesulfonate



To a stirred solution of 2-methoxypropane-1,3-diol (190 mg, 1.790 mmol) in DCM (5 mL) under a nitrogen atmosphere, TEA (1.497 mL, 10.74 mmol) was added at 0 °C. To this reaction mixture, methanesulfonyl chloride (0.349 mL, 4.48 mmol) was added. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was quenched with saturated $NaHCO_3$ solution (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 2-methoxypropane-1,3-diyl dimethanesulfonate (450 mg, 96% yield) as a semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 - 4.34 (m, 2H), 4.26 - 4.21 (m, 2H), 3.82 - 3.76 (m, 1H), 3.40 (s, 3H), 3.23 (s, 6H). This material was used without further purification.

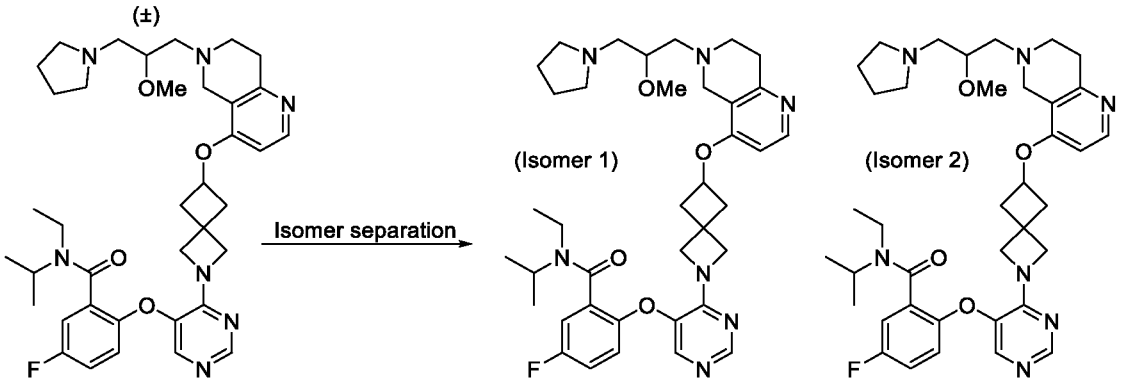
Step 3. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (400 mg, 0.686 mmol) in acetonitrile (5 mL), TEA (0.574 mL, 4.12 mmol) was added at RT. To this reaction mixture, pyrrolidine (0.056 mL, 0.686 mmol) and 2-methoxypropane-1,3-diyl dimethanesulfonate (450 mg, 1.715 mmol) were added. The reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure. The residue was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) followed by achiral SFC (method D) to obtain (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (12.85 mg, 2.70% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.20 - 8.17 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.68 - 6.65 (m, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.05 (m, 5H), 3.83 - 3.70 (m, 1H), 3.49 (s, 3H), 3.44 - 3.36 (m, 1H), 3.28 - 3.18 (m, 2H), 2.83 - 2.73 (m, 5H), 2.65 - 2.55 (m, 4H), 2.54 - 2.52 (m, 3H), 2.49 - 2.46 (m, 3H), 2.30 - 2.20 (m, 2H), 1.74 - 1.60 (m, 4H), 1.14 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.83 min, m/z = 688.4 $[M+H]^+$; HPLC (Method A): Rt = 5.04 min, 97.56%. Chiral SFC (Method J): Peak 1: Rt = 5.50 min, 50.19%; Peak 2: Rt = 6.20 min, 49.81%.

Example 141. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 259)

Example 142. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 260)



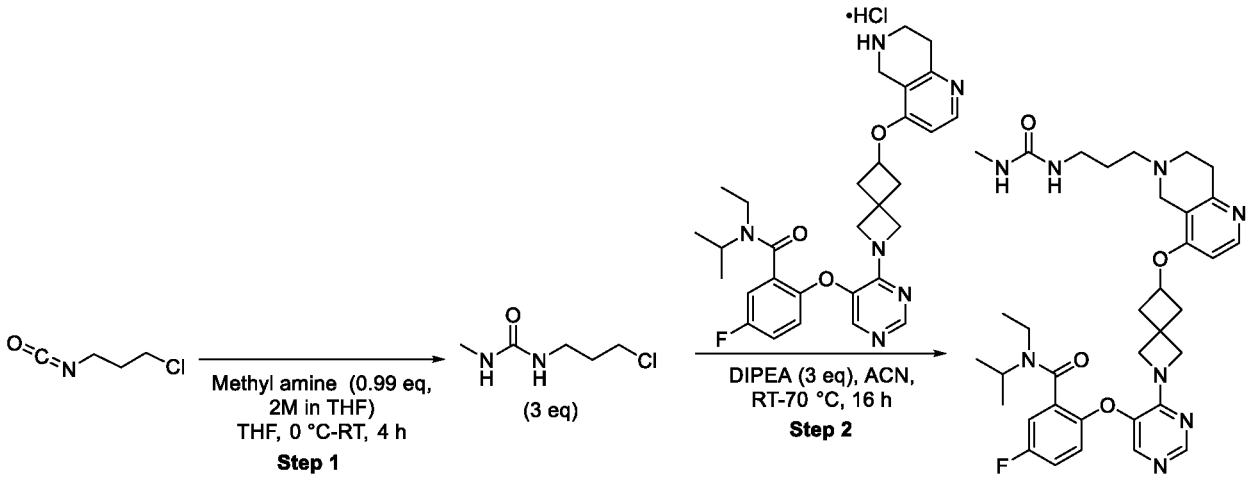
(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (200 mg, 0.291 mmol) was purified by chiral Prep SFC (Method C) to obtain both isomers, (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (36.58 mg, 18.09% yield) and (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-methoxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (28.03 mg, 13.93 % yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.21 - 8.15 (m, 1H), 7.77 - 7.64 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.79 - 4.70 (m, 1H), 4.46 - 4.05 (m, 4H), 3.80 - 3.70 (m, 1H), 3.48 (s, 3H), 3.46 - 3.37 (m, 2H), 3.29 - 3.20 (m, 2H), 2.82 - 2.74 (m, 5H), 2.54-2.64 (m, 4H), 2.47 - 2.42 (m, 6H), 2.29 - 2.21 (m, 2H), 1.62-1.69 (m, 4H), 1.14 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.97 min, m/z = 688.4 $[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 98.90% Chiral SFC (Method AH): RT = 13.35 min, 98.19%.

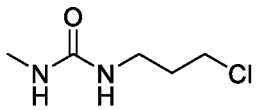
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.78 - 4.70 (m, 1H), 4.47 - 4.06 (m, 4H), 3.80 - 3.71 (m, 1H), 3.49 (s, 3H), 3.46 - 3.37 (m, 2H), 3.28 - 3.18 (m, 2H), 2.83 - 2.74 (m, 5H), 2.65 - 2.55 (m, 4H), 2.48 - 2.45 (m, 6H), 2.29 - 2.21 (m, 2H),

1.69 - 1.63 (m, 4H), 1.14- 0.98 (m, 9H); LCMS (Method G): Rt = 1.85 min, m/z = 688.4 $[M+H]^+$; HPLC (Method A): Rt = 5.12 min, 99.39%; Chiral SFC (Method AH): RT = 15.22 min, 96.39%.

Example 143. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methylureido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 143)

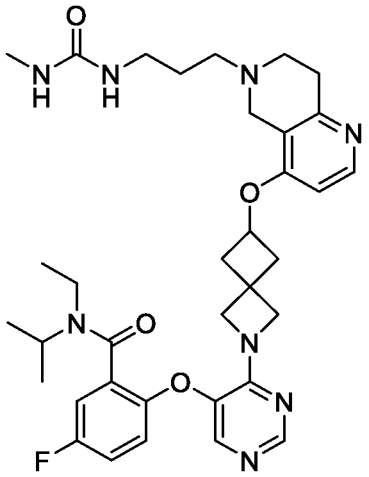


Step 1. 1-(3-Chloropropyl)-3-methylurea



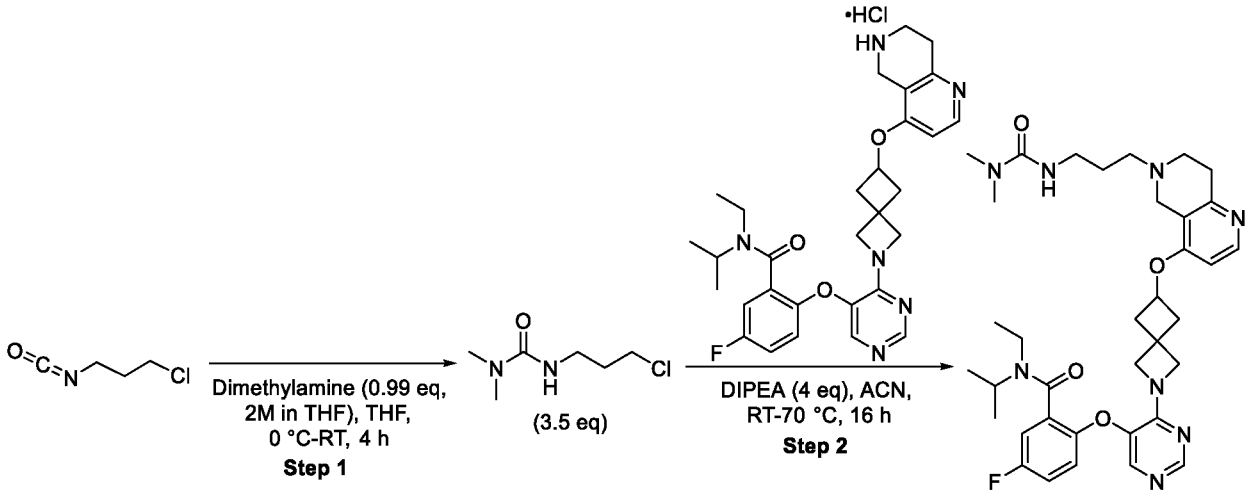
To a stirred solution of 1-chloro-3-isocyanatopropane (500 mg, 4.18 mmol) in THF (8 mL), methylamine 2.070 mL, 4.14 mmol, 2M in THF) was added at 0 °C. The reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure, and the residue was washed with MTBE (10 mL) to afford crude 1-(3-chloropropyl)-3-methylurea (450 mg, 65.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.98 (t, J = 5.8 Hz, 1H), 5.69 (q, J = 4.8 Hz, 1H), 3.62 (t, J = 6.5 Hz, 2H), 3.09 (q, J = 6.6 Hz, 2H), 2.53 (d, J = 4.7 Hz, 3H), 1.81 (quin, J = 6.6 Hz, 2H); LCMS (Method G): Rt = 0.84 min, m/z = 151.2 $[M+H]^+$, 92.71%. This material was used without further purification.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methylureido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

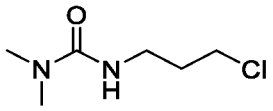


To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (200 mg, 0.343 mmol) in ACN (5 mL), DIPEA (0.179 mL, 1.029 mmol) and 1-(3-chloropropyl)-3-methylurea (155 mg, 1.029 mmol) were added at RT. The reaction was stirred at 70 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methylureido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (93.44 mg, 41.0% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 - 8.42 (m, 1H), 8.28 (d, *J* = 5.6 Hz, 1H), 7.89 - 7.82 (m, 1H), 7.09 - 7.00 (m, 2H), 6.76 - 6.69 (m, 1H), 6.41 (d, *J* = 5.6 Hz, 1H), 5.36 - 5.13 (m, 1H), 5.10 - 4.91 (m, 1H), 4.66 (quin, *J* = 6.7 Hz, 1H), 4.43 - 4.13 (m, 4H), 3.95 - 3.84 (m, 1H), 3.58 - 3.45 (m, 2H), 3.44 - 3.35 (m, 1H), 3.35 - 3.29 (m, 2H), 3.27 - 3.17 (m, 1H), 3.05 - 2.98 (m, 2H), 2.85 - 2.72 (m, 4H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.60 (d, *J* = 4.8 Hz, 3H), 2.49 - 2.34 (m, 2H), 1.81 (quin, *J* = 6.0 Hz, 2H), 1.36 - 1.08 (m, 9H); LCMS (Method G): Rt = 1.53 min, m/z = 661.6 $[M+H]^+$; HPLC (Method A): Rt = 4.59 min, 98.35%.

Example 144. 2-((4-(6-((6-(3-(3,3-Dimethylureido)propyl)-5,6,7,8-Tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 148)



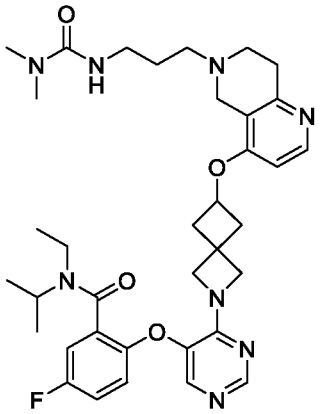
Step 1. 3-(3-Chloropropyl)-1,1-dimethylurea



This compound was synthesized following the procedure described for the synthesis of Example 143, step 1, starting with 1-chloro-3-isocyanatopropane, except that 0.99 equivalent of dimethylamine (2M in THF) was used. After completion, the reaction was concentrated under reduced pressure to afford crude 3-(3-chloropropyl)-1,1-dimethylurea.

Yield: 99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.74 - 4.39 (br s, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.48 - 3.31 (m, 2H), 2.93 (s, 6H), 2.03 (quin, J = 6.4 Hz, 2H); LCMS (Method G): Rt = 1.09 min, m/z = 165.2 $[M+H]^+$, 98.29%. This material was used without further purification.

Step 2. 2-((4-(6-((6-(3-(3,3-Dimethylureido)propyl)-5,6,7,8-Tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



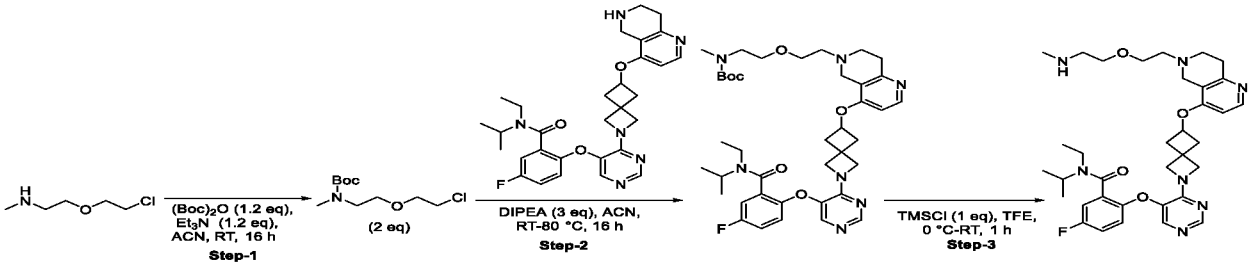
This compound was synthesized following the procedure described for the synthesis of Example 143, step 2, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-

yl)oxy)benzamide hydrochloride, except that 3.5 equivalents of 3-(3-chloropropyl)-1,1-dimethylurea, 4 equivalents of DIPEA were used. After completion, the reaction was concentrated under reduced pressure. The residue was quenched with water and extracted with EtOAc. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by Prep HPLC (Method AG) to afford 2-((4-(6-((6-(3-(3,3-dimethylureido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

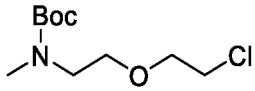
Yield: 9.01%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.10 - 7.01 (m, 1H), 6.70 - 6.63 (m, 1H), 4.79 - 4.71 (m, 1H), 4.31 - 4.07 (m, 4H), 3.80 - 3.72 (m, 1H), 3.46 - 3.37 (m, 4H), 3.27 - 3.11 (m, 2H), 3.10 - 3.02 (m, 2H), 2.84 - 2.75 (m, 4H), 2.73 (s, 6H), 2.71 - 2.65 (m, 3H), 2.31 - 2.22 (m, 2H), 1.70 - 1.59 (m, 2H), 1.28 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.64 min, m/z = 675.7 $[M+H]^+$; HPLC (Method A): Rt = 4.83 min, 98.18%.

Example 145. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(2-(methylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 216)



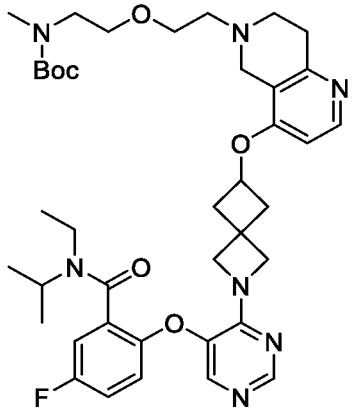
Step 1. tert-Butyl (2-(2-chloroethoxy)ethyl)(methyl)carbamate



To a stirred solution of 2-(2-chloroethoxy)-*N*-methylethan-1-amine (0.35 g, 2.54 mmol) in ACN (5 mL), triethylamine (0.386 mL, 3.05 mmol) was added at RT. To this reaction mixture, $(Boc)_2O$ (0.666 g, 3.05 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with water (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous

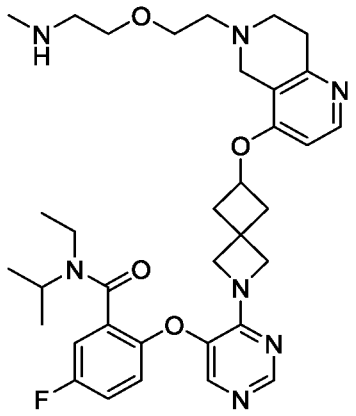
sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude *tert*-butyl (2-(2-chloroethoxy)ethyl)(methyl)carbamate (0.5 g, 44.7% yield) as semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 - 3.70 (m, 2H), 3.66 - 3.59 (m, 4H), 3.48 - 3.37 (m, 2H), 2.94 (s, 3H), 1.48 (s, 9H); LCMS (Method G): Rt = 1.83 min, m/z = 138.2 $[M-100]^+$, 54.74%. This material was used without further purification.

Step 2. tert-Butyl (2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethoxy)ethyl)(methyl)carbamate



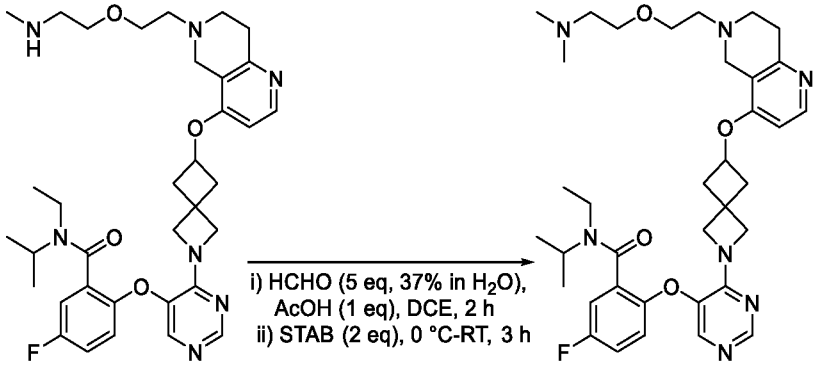
To a solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.3 g, 0.549 mmol) in ACN (5 mL), DIPEA (0.266 mL, 1.646 mmol) was added at RT. To this reaction mixture, *tert*-butyl (2-(2-chloroethoxy)ethyl)(methyl)carbamate (0.261 g, 1.098 mmol) was added, and the reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced, quenched with water (25 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *tert*-butyl (2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethoxy)ethyl)(methyl)carbamate (180 mg, 4.39% yield) as a solid. LCMS (Method G): Rt = 2.13 min, m/z = 748.5 $[M+H]^+$, 89.86%.

Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(2-(methylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



In a 100 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl (2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethoxy)ethyl)(methyl)carbamate (180 mg, 0.241 mmol) was added in 2,2,2-trifluoroethanol (10 mL). TMSCl (0.03 mL, 0.241 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 1 h. The progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(2-(methylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by achiral Prep SFC (Method B) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(2-(methylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (13 mg, 8.25% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.19 - 8.16 (m, 1H), 7.77 - 7.67 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 6.99 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.47 - 4.04 (m, 4H), 3.82 - 3.69 (m, 1H), 3.58 (t, J = 5.6 Hz, 2H), 3.51 - 3.46 (m, 4H), 3.25 - 3.12 (m, 2H), 2.83 - 2.73 (m, 5H), 2.72 - 2.64 (m, 6H), 2.30 (s, 3H), 2.28 - 2.21 (m, 2H), 1.16 - 0.95 (m, 9H); LCMS (Method C): Rt = 1.77 min, m/z = 648.4 $[M+H]^+$; HPLC (Method A): Rt = 4.68 min, 98.99%.

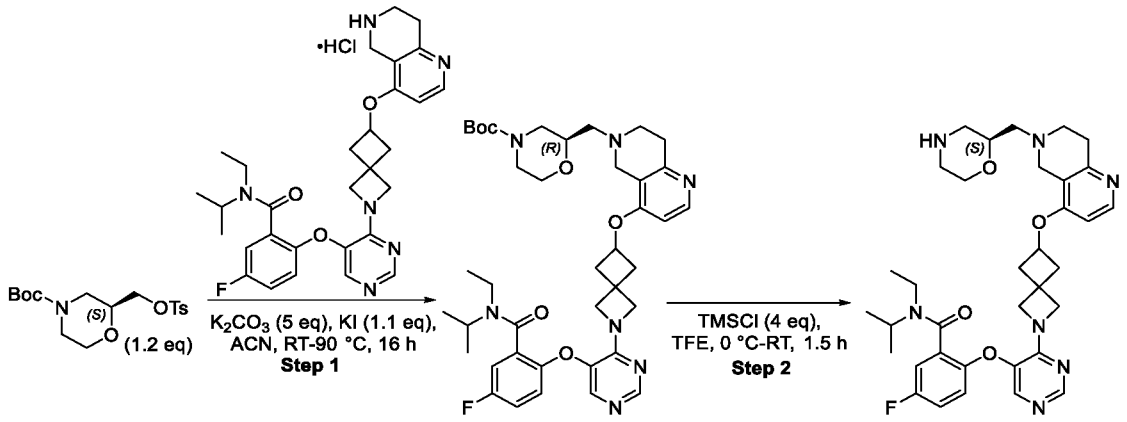
Example 146. 2-((4-(6-((6-(2-(2-(Dimethylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 232)



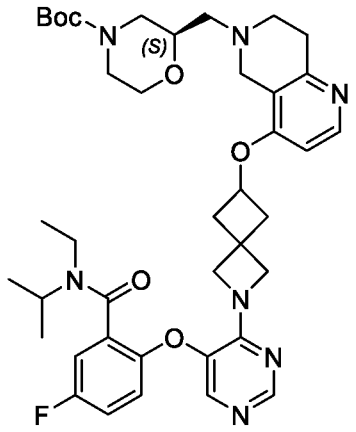
This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(2-(methylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-(2-(2-(dimethylamino)ethoxy)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 44.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.19 - 8.16 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.46 - 4.07 (m, 5H), 3.79 - 3.71 (m, 1H), 3.57 (t, *J* = 5.7 Hz, 2H), 3.52 - 3.45 (m, 5H), 2.83 - 2.72 (m, 6H), 2.68 (t, *J* = 5.7 Hz, 2H), 2.40 (t, *J* = 5.9 Hz, 2H), 2.36 - 2.21 (m, 2H), 2.14 (s, 6H), 1.17 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.76 min, m/z = 662.4 $[M+H]^+$; HPLC (Method A): Rt = 4.71 min, 98.54%.

Example 147. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 217)

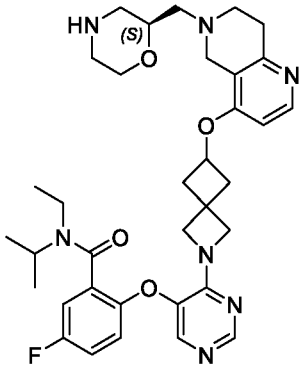


Step 1. tert-Butyl (R)-2-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate



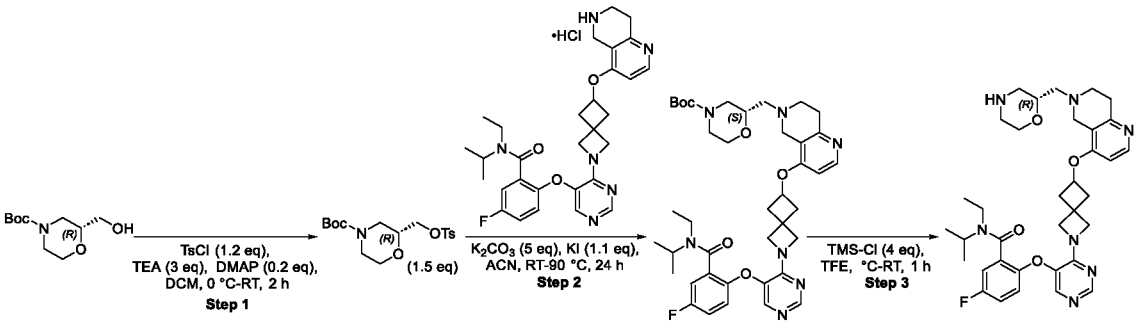
To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (500 mg, 0.857 mmol) in ACN (8 mL), powdered K_2CO_3 (593 mg, 4.29 mmol) was added at RT. To this solution, KI (157 mg, 0.943 mmol) and *tert*-butyl (*S*)-2-((tosyloxy)methyl)morpholine-4-carboxylate (382 mg, 1.029 mmol) were added. The reaction was stirred at 90 °C for 16 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (*R*)-2-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate (270 mg, 38.4% yield) as a solid. LCMS (Method G): Rt = 1.97 min, m/z = 746.7 $[M+H]^+$, 96.94%.

Step 2. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

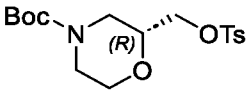


To a stirred solution of *tert*-butyl (*R*)-2-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate (50 mg, 0.067 mmol) in 2,2,2-trifluoroethanol (1 mL), TMSCl (0.034 mL, 0.268 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (14 mg, 31.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.19 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.47 - 4.08 (m, 4H), 3.79 - 3.67 (m, 2H), 3.59 - 3.51 (m, 1H), 3.46 - (br s, 2H), 3.45 - 3.37 (m, 2H), 3.29 - 3.21 (m, 1H), 2.84 - 2.74 (m, 6H), 2.70 - 2.62 (m, 4H), 2.49 - 2.46 (m, 2H), 2.36 - 2.31 (m, 1H), 2.30 - 2.22 (m, 2H), 1.14 - 0.98 (m, 9H); LCMS (Method D): Rt = 1.65 min, m/z = 646.4 $[M+H]^+$; HPLC (Method A): Rt = 4.58 min, 96.71%; Chiral SFC (Method AN): Rt = 1.86 min, 98.45%.

Example 148. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (compound No. 218)



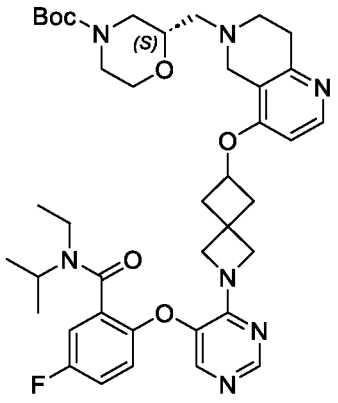
Step 1. tert-Butyl (R)-2-((tosyloxy)methyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 42, starting with 1 equivalent of *tert*-butyl (*R*)-2-(hydroxymethyl)morpholine-4-carboxylate. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 10-15% EtOAc in hexane) to obtain *tert*-butyl (*R*)-2-((tosyloxy)methyl)morpholine-4-carboxylate as a solid.

Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 - 7.80 (m, 2H), 7.39 - 7.35 (m, 2H), 4.08 - 3.99 (m, 2H), 3.95 - 3.77 (m, 3H), 3.67 - 3.58 (m, 1H), 3.53 - 3.44 (m, 1H), 2.98 - 2.85 (m, 1H), 2.77 - 2.62 (m, 1H), 2.47 (s, 3H), 1.48 (s, 9H); LCMS (Method G): Rt = 2.06 min, m/z = 272.2 $[M-100]^+$, 99.10%.

Step 2. tert-Butyl (S)-2-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate

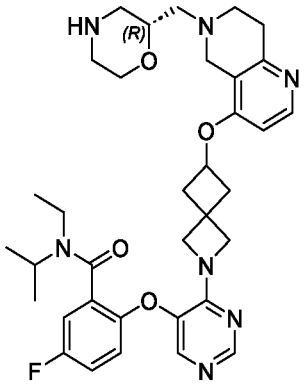


This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents of *tert*-butyl (*R*)-2-((tosyloxy)methyl)morpholine-4-carboxylate was used. The crude product was purified by

reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (*S*)-2-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate as a semi-solid.

Yield: 38.2%; LCMS (Method C): Rt = 2.22 min, m/z = 746.4 $[M+H]^+$, 97.76%.

Step 3. (R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

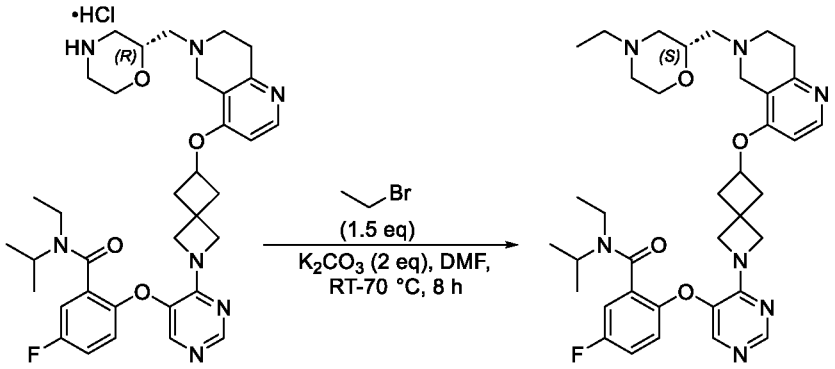


This compound was synthesized following the procedure described for the synthesis of Example 147, step 2, starting with *tert*-butyl (*S*)-2-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 35.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.79 - 3.67 (m, 2H), 3.60 - 3.51 (m, 1H), 3.46 (br s, 2H), 3.44 - 3.37 (m, 2H), 3.27 - 3.20 (m, 1H), 2.84 - 2.74 (m, 6H), 2.71 - 2.62 (m, 4H), 2.49 - 2.46 (m, 2H), 2.36 - 2.31 (m, 1H), 2.30 - 2.21 (m, 2H), 1.14 - 0.96 (m, 9H); LCMS (Method D): Rt =

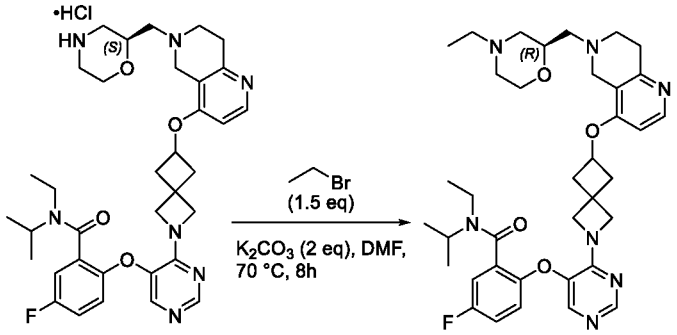
1.65 min, m/z = 646.4 $[M+H]^+$; HPLC (Method A): Rt = 4.58 min, 98.36%; Chiral SFC (Method AN): Rt = 1.91 min, 95.96%.

Example 149. (*S*)-*N*-Ethyl-2-((4-(6-((6-((4-ethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 254)



To a stirred solution of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (220 mg, 0.322 mmol) in DMF (8 mL), powdered K_2CO_3 (89 mg, 0.645 mmol) was added at RT. Bromoethane (52.7 mg, 0.484 mmol) was added to this reaction mixture. The reaction was stirred at 70 °C for 8 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT, quenched with ice-cold water (10 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-ethyl-2-((4-(6-((6-((4-ethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (48.44 mg, 22.25% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.68 - 6.64 (m, 1H), 4.78 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.80 - 3.72 (m, 2H), 3.68 - 3.61 (m, 1H), 3.54 - 3.49 (m, 1H), 3.47 (br s, 2H), 3.44 - 3.37 (m, 1H), 3.31 - 3.13 (m, 3H), 2.84 - 2.74 (m, 6H), 2.71 - 2.66 (m, 2H), 2.32 - 2.22 (m, 4H), 1.98 - 1.90 (m, 1H), 1.72 (t, J = 10.7 Hz, 1H), 1.16 - 0.95 (m, 12H); LCMS (Method G): Rt = 1.89 min, m/z = 674.5$[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 99.83%; Chiral SFC (Method AK): Rt = 1.43 min, 95.64%.

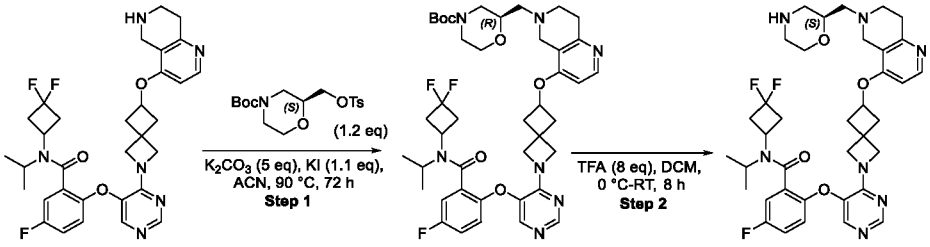
Example 150. (*R*)-*N*-Ethyl-2-((4-(6-((6-((4-ethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 255)



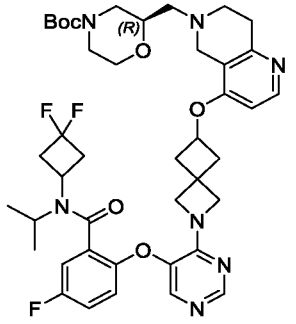
This compound was synthesized following the procedure described for the synthesis of Example 149, starting with 1 equivalent of (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.5 equivalent of bromoethane. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-2-((4-(6-((6-((4-ethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide.

Yield: 8.54%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.21 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.79 - 4.70 (m, 1H), 4.47 - 4.06 (m, 4H), 3.81 - 3.70 (m, 2H), 3.68 - 3.60 (m, 1H), 3.54 - 3.49 (m, 1H), 3.47 (br s, 2H), 3.44 - 3.38 (m, 1H), 3.29 - 3.11 (m, 3H), 2.84 - 2.74 (m, 6H), 2.71 - 2.65 (m, 2H), 2.33 - 2.22 (m, 4H), 1.98 - 1.89 (m, 1H), 1.72 (t, J = 10.6 Hz, 1H), 1.15 - 0.95 (m, 12H); LCMS (Method G): Rt = 1.86 min, m/z = 674.7 $[M+H]^+$; HPLC (Method D): Rt = 2.02 min, 98.92%; Chiral SFC (Method AK): Rt = 1.42 min, 99.23%.

Example 151. (*S*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 246)



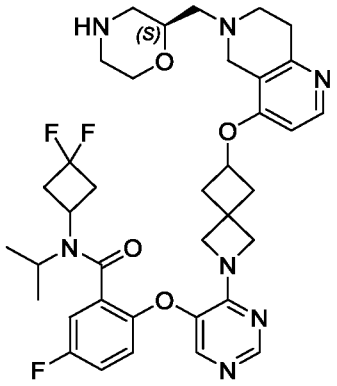
Step 1. tert-Butyl (R)-2-((4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *tert*-butyl (*S*)-2-((tosyloxy)methyl)morpholine-4-carboxylate, except that 1 equivalent of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide was used. After completion, the reaction was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM) to afford *tert*-butyl (*R*)-2-((4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate as a solid.

Yield: 50.3%; LCMS (Method G): Rt = 2.18 min, m/z = 808.7 $[M+H]^+$; 89.02%.

Step 2. (S)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

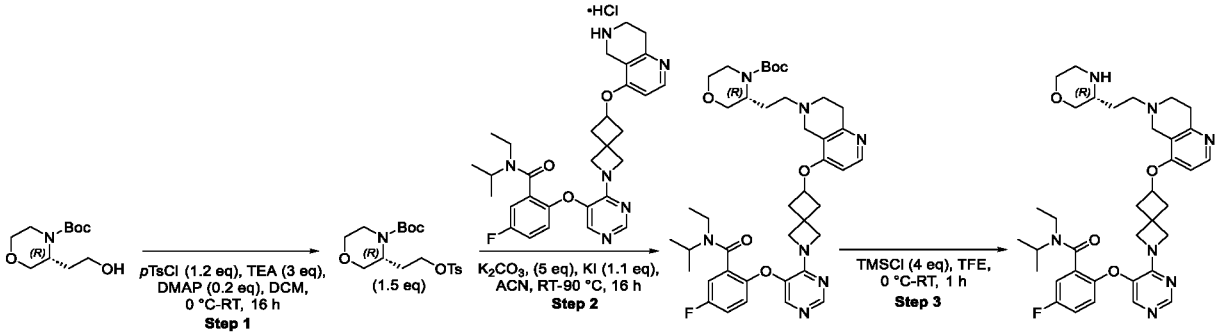


This compound was synthesized following the procedure described for the synthesis of Example 147, step 2, starting with *tert*-butyl (*R*)-2-((4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-

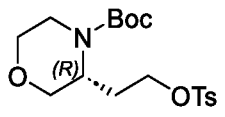
azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)morpholine-4-carboxylate, except that 8 equivalents of TFA was used and DCM was used as the solvent. After completion, the reaction was concentrated under reduced pressure. Ice water was added to the residue, and the mixture was washed with saturated sodium bicarbonate solution, then extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain (*S*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide trifluoroacetate (410 mg, 89% yield). The crude product (100 mg) was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*S*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid (70.38 mg).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.33 (m, 1H), 7.31 - 7.22 (m, 1H), 7.06 (br dd, *J* = 3.9, 8.7 Hz, 1H), 6.65 (d, *J* = 5.6 Hz, 1H), 4.74 (quin, *J* = 6.4 Hz, 1H), 4.31 - 4.07 (m, 4H), 3.97 - 3.90 (m, 1H), 3.80 - 3.68 (m, 3H), 3.60 - 3.49 (m, 2H), 3.46 (s, 2H), 3.43 - 3.38 (m, 2H), 2.84 - 2.59 (m, 12H), 2.36 - 2.22 (m, 4H), 1.14 - 0.96 (m, 6H); LCMS (Method J): Rt = 1.41 min, m/z = 708.4 $[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 97.34%; Chiral SFC (Method AI): Rt = 1.16 min, 95.78%.

Example 152. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 268)



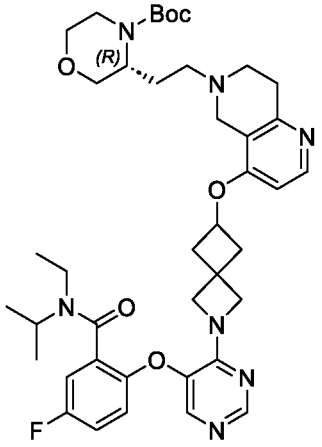
Step 1. tert-Butyl (R)-3-(2-(tosyloxy)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 42, starting with 1 equivalent of *tert*-butyl (*R*)-3-(2-hydroxyethyl)morpholine-4-carboxylate. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 25-30% EtOAc in hexane) to obtain *tert*-butyl (*R*)-3-(2-(tosyloxy)ethyl)morpholine-4-carboxylate as a semi-solid.

Yield: 88%; LCMS (Method G): Rt = 2.13 min, m/z = 286.2 $[M-100]^+$, 98.23%.

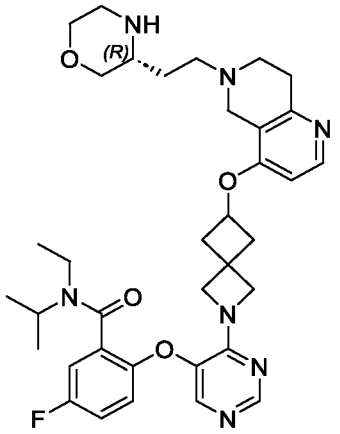
Step 2. tert-Butyl (R)-3-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents of *tert*-butyl (*R*)-3-(2-(tosyloxy)ethyl)morpholine-4-carboxylate was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (*R*)-3-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate as a solid.

Yield: 53.0%; LCMS (Method G): Rt = 2.23 min, m/z = 760.5 $[M+H]^+$, 98.65%.

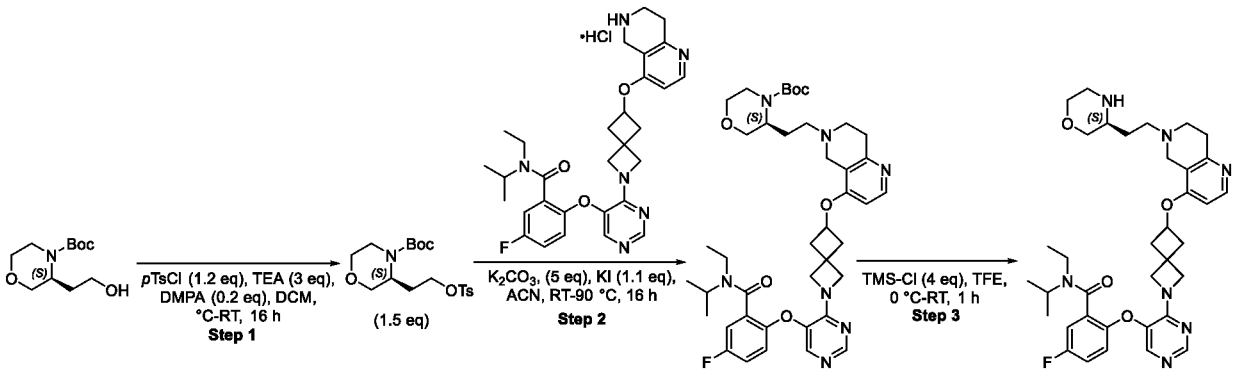
Step 3. (R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



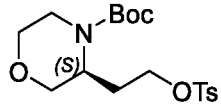
This compound was synthesized following the procedure described for the synthesis of Example 147, step 2, starting with *tert*-butyl (*R*)-3-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 33.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.65 (m, 1H), 4.79 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.80 - 3.72 (m, 1H), 3.69 - 3.59 (m, 2H), 3.46 - 3.36 (m, 3H), 3.28 - 3.12 (m, 2H), 3.01 (t, *J* = 10.3 Hz, 1H), 2.83 - 2.75 (m, 6H), 2.73 - 2.63 (m, 6H), 2.31 - 2.22 (m, 2H), 1.43 (q, *J* = 7.2 Hz, 2H), 1.14 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.60 min, m/z = 660.6 $[M+H]^+$; HPLC (Method A): Rt = 4.68 min, 99.64%, Chiral SFC (Method K): Rt = 4.49 min, 96.31%.

Example 153. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 275)



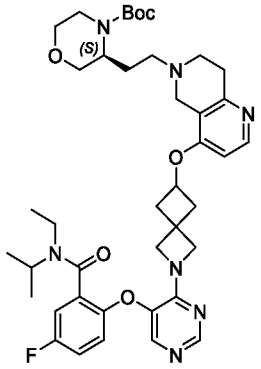
Step 1. tert-Butyl (S)-3-(2-(tosyloxy)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 42, starting with 1 equivalent of *tert*-butyl (*S*)-3-(2-hydroxyethyl)morpholine-4-carboxylate. The crude was purified by silica gel flash column chromatography using 50% EtOAc in hexane to obtain *tert*-butyl (*S*)-3-(2-(tosyloxy)ethyl)morpholine-4-carboxylate as a solid.

Yield: 78%; LCMS (Method G): Rt = 2.15 min, m/z = 286.2 $[M-100]^+$, 99.39%.

Step 2. tert-Butyl (S)-3-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate

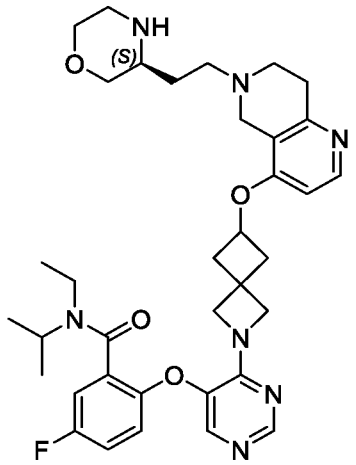


This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents *tert*-butyl (*S*)-3-(2-(tosyloxy)ethyl)morpholine-4-carboxylate was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-

butyl (*S*)-3-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate a semi-solid.

Yield: 30%; LCMS (Method G): Rt = 2.03 min, m/z = 760.8 $[M+H]^+$, 97.81%.

Step 3. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

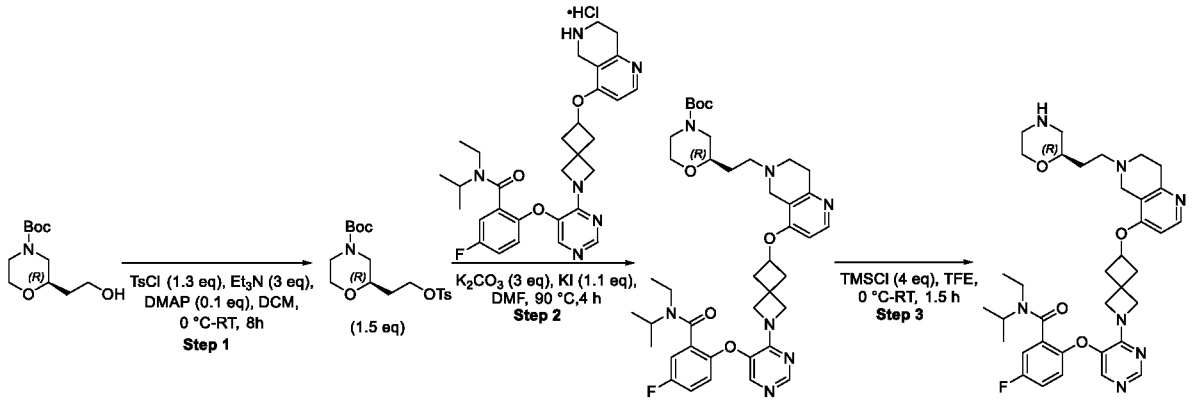


This compound was synthesized following the procedure described for the synthesis of Example 147, step 2, starting with *tert*-butyl (*S*)-3-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

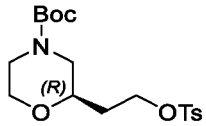
Yield: 36.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.20 (m, 2H), 7.11 - 6.98 (m, 1H), 6.70 - 6.63 (m, 1H), 4.79 - 4.68 (m, 1H), 4.46 - 4.06 (m, 4H), 3.79 - 3.71 (m, 1H), 3.69 - 3.58 (m, 2H), 3.44 - 3.39 (m, 3H), 3.28 - 3.21 (m, 2H), 3.01 (t, *J* = 10.3 Hz, 1H), 2.83 - 2.74 (m, 6H), 2.72 - 2.63 (m, 6H), 2.31 - 2.22 (m, 2H), 1.43 (q, *J* = 7.0 Hz, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.67

min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.68 min, 99.25%; Chiral SFC (Method K): Rt = 6.58 min, 99.70%.

Example 154. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 276)



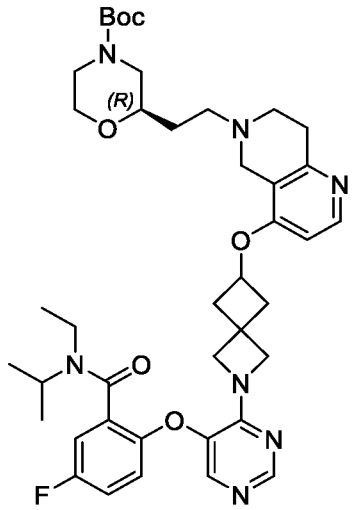
Step 1. tert-Butyl (R)-2-(2-(tosyloxy)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 42, starting with 1 equivalent of *tert*-butyl (*R*)-2-(2-hydroxyethyl)morpholine-4-carboxylate, except that 1.3 equivalents of *p*-TsCl and 0.1 equivalent of DMAP were used. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain *tert*-butyl (*R*)-2-(2-(tosyloxy)ethyl)morpholine-4-carboxylate.

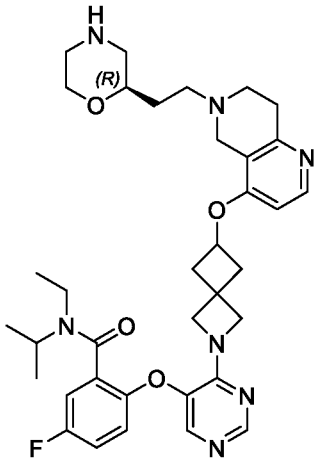
Yield: 71.8%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 - 7.78 (m, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 4.24 - 4.12 (m, 2H), 3.93 - 3.81 (m, 2H), 3.79 - 3.72 (m, 1H), 3.48 - 3.33 (m, 2H), 2.94 - 2.76 (m, 1H), 2.63 - 2.51 (m, 1H), 2.48 (s, 3H), 1.89 - 1.79 (m, 1H), 1.78 - 1.66 (m, 1H), 1.48 (s, 9H); LCMS (Method B): Rt = 2.24 min, m/z = 286.2 $[M+H]^+$, 99.75%.

Step 2. tert-Butyl (R)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents of *tert*-butyl (*R*)-2-(2-(tosyloxy)ethyl)morpholine-4-carboxylate and 3 equivalents of powdered K_2CO_3 were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain *tert*-butyl (*R*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate. Yield: 34.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.18 (br d, J = 5.7 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.66 (br d, J = 5.5 Hz, 1H), 4.82 - 4.68 (m, 1H), 4.33 - 4.06 (m, 4H), 3.89 - 3.64 (m, 4H), 3.50 - 3.37 (m, 4H), 3.27 - 3.12 (m, 2H), 2.92 - 2.64 (m, 7H), 2.62 - 2.55 (m, 3H), 2.32 - 2.22 (m, 2H), 1.72 - 1.57 (m, 2H), 1.38 (br s, 9H), 1.17 - 0.95 (m, 9H); LCMS (Method B): Rt = 1.30 min, m/z = 760.4 $[M+H]^+$, 94.07%.

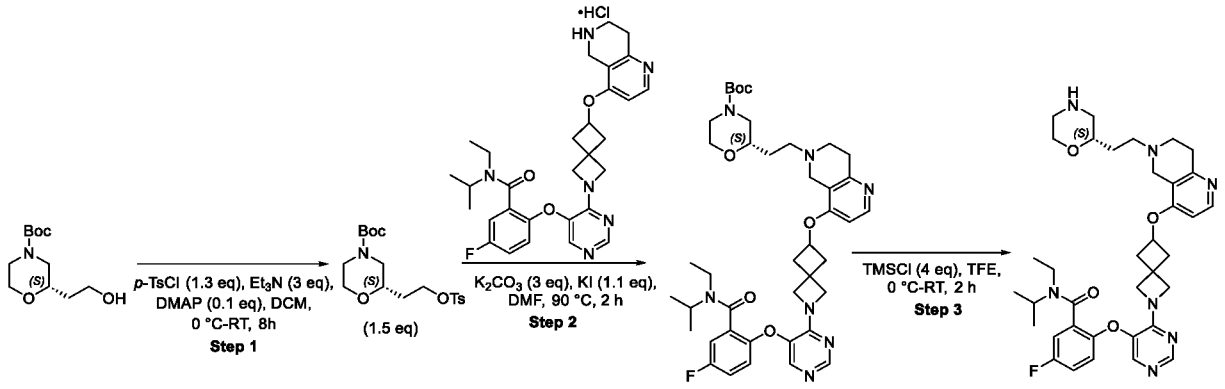
Step 3. (R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



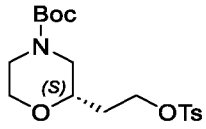
This compound was synthesized following the procedure described for the synthesis of Example 147, step 2, starting with *tert*-butyl (*R*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield:43.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.80 - 7.59 (m, 1H), 7.36 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.66 (d, J = 5.5 Hz, 1H), 4.84 - 4.63 (m, 1H), 4.34 - 4.06 (m, 4H), 3.84 - 3.59 (m, 2H), 3.47 - 3.37 (m, 4H), 3.28 - 3.14 (m, 2H), 2.86 - 2.73 (m, 5H), 2.71 - 2.56 (m, 6H), 2.38 - 2.22 (m, 4H), 1.62 - 1.48 (m, 2H), 1.29 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.66 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 97.09%, Chiral SFC (Method AV): Rt = 8.24 min, 98.56%.

Example 155. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 277)



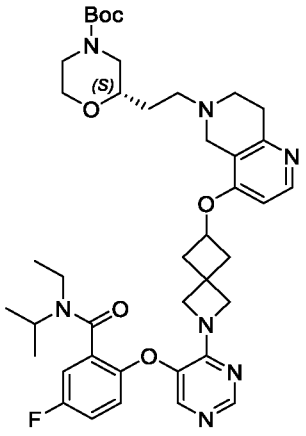
Step 1. tert-Butyl (S)-2-(2-(tosyloxy)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Intermediate 42, starting with 1 equivalent of *tert*-butyl (*S*)-2-(2-hydroxyethyl)morpholine-4-carboxylate, except that 1.3 equivalents of *p*-TsCl and 0.1 equivalent of DMAP were used. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain *tert*-butyl (*S*)-2-(2-(tosyloxy)ethyl)morpholine-4-carboxylate as a solid.

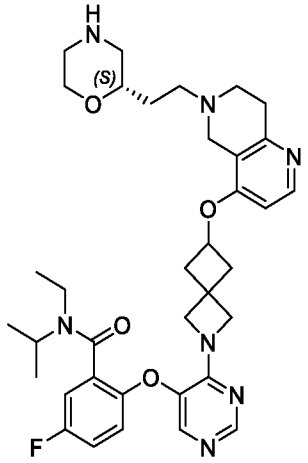
Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.26 - 4.11 (m, 2H), 3.95 - 3.79 (m, 2H), 3.75 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.48 - 3.32 (m, 2H), 2.98 - 2.79 (m, 1H), 2.66 - 2.52 (m, 1H), 2.48 (s, 3H), 1.90 - 1.69 (m, 2H), 1.48 (s, 9H); LCMS (Method B): Rt = 2.24 min, m/z = 286.2 $[M+H-100]^+$, 99.53%.

Step 2. tert-Butyl (S)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents of *tert*-butyl (*S*)-2-(2-(tosyloxy)ethyl)morpholine-4-carboxylate and 3 equivalents of powdered K_2CO_3 were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain *tert*-butyl (*S*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate as a solid. Yield: 26.3%; LCMS (Method B): Rt = 1.33 min, m/z = 761.4 $[M+H]^+$, 68.52%.

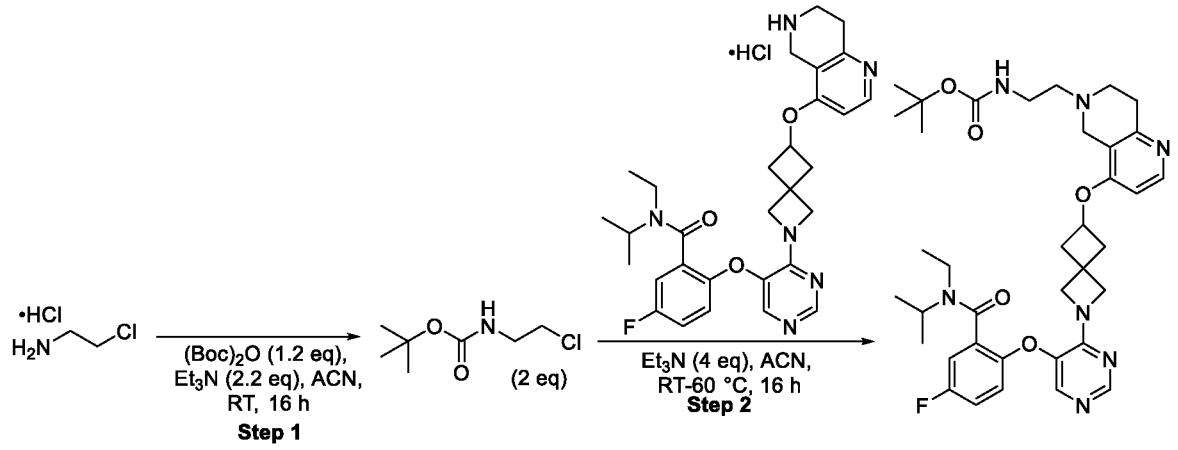
Step 3. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



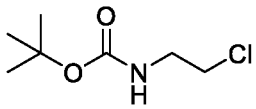
This compound was synthesized following the procedure described for the synthesis of Example 147, step 2, starting with *tert*-butyl (*S*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)morpholine-4-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield:31.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.01 (m, 1H), 6.69 - 6.62 (m, 1H), 4.80 - 4.70 (m, 1H), 4.33 - 4.06 (m, 4H), 3.80 - 3.65 (m, 2H), 3.46 - 3.36 (m, 4H), 3.26 - 3.10 (m, 1H), 2.85 - 2.74 (m, 5H), 2.71 - 2.58 (m, 5H), 2.40 - 2.21 (m, 6H), 1.61 - 1.51 (m, 2H), 1.24 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.66 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 98.55%; Chiral SFC (Method AJ): Rt = 4.41 min, 98.55%.

Example 156. *tert*-Butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)carbamate (Compound No. 142)

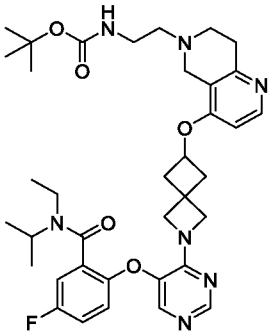


Step 1. tert-Butyl (2-chloroethyl)carbamate



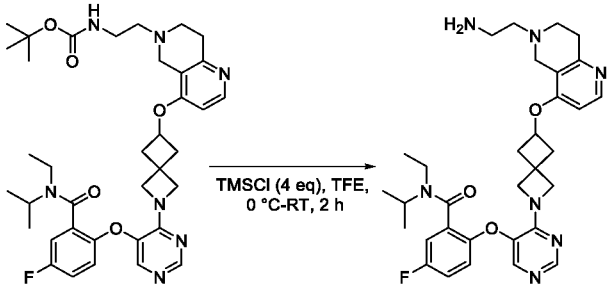
To a stirred solution of 2-chloroethan-1-amine hydrochloride (1.5 g, 12.93 mmol) in acetonitrile (5 mL), triethylamine (3.97 mL, 28.5 mmol) was added at RT. To this reaction mixture, $(Boc)_2O$ (3.57 mL, 15.52 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was quenched with water (25 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 30% EtOAc in hexane) to obtain *tert*-butyl (2-chloroethyl)carbamate (1.1 g, 47.3% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05 (s, 1H), 3.56 (t, J = 6.4 Hz, 2H), 3.23 (q, J = 6.2 Hz, 2H), 1.39 (s, 9H).

Step 2. tert-Butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)carbamate



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.15 g, 0.274 mmol) in acetonitrile (5 mL), TEA (0.153 mL, 1.098 mmol) was added at RT. To this reaction mixture, *tert*-butyl (2-chloroethyl)carbamate (0.099 g, 0.549 mmol) was added, and the reaction was stirred at 60 °C for 16 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)carbamate (50 mg, 26.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 6.98 (m, 1H), 6.76 - 6.55 (m, 2H), 4.80 - 4.69 (m, 1H), 4.52 - 3.94 (m, 4H), 3.75 - 3.78 (m, 1H), 3.45 (br s, 2H), 3.39- 3.37 (m, 1H), 3.29 - 3.18 (m, 1H), 3.18 - 3.01 (m, 2H), 2.83 - 2.64 (m, 6H), 2.59 - 2.52 (m, 2H), 2.32 - 2.22 (m, 2H), 1.37 (s, 9H), 1.26 - -0.87 (m, 9H); LCMS (Method G): Rt = 1.95 min, m/z = 690.4 $[M+H]^+$; HPLC (Method A): Rt = 5.95 min, 99.27%.

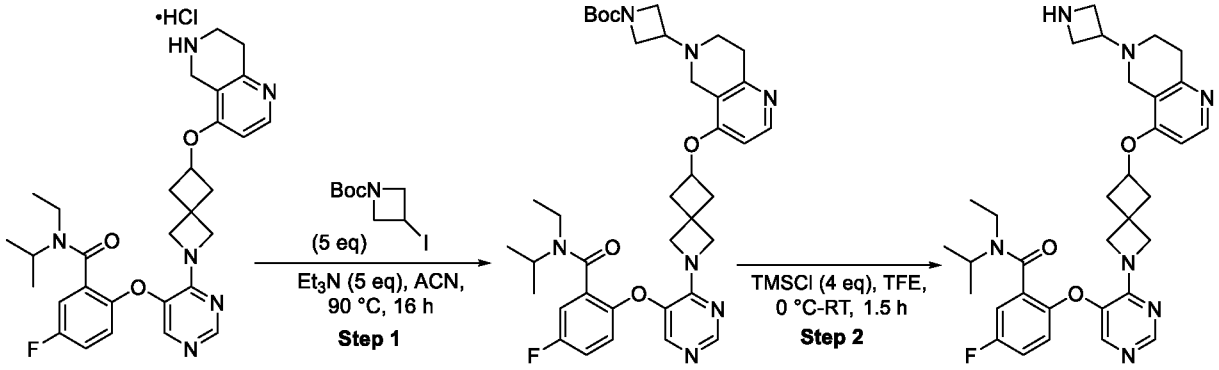
Example 157. 2-((4-(6-((6-(2-Aminoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 159)



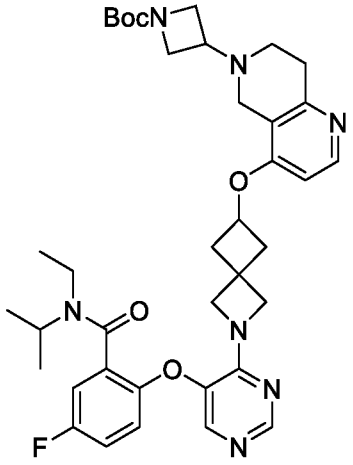
To a stirred solution of *tert*-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-

naphthyridin-6(5H)-yl)ethyl)carbamate (0.1 g, 0.145 mmol) in 2,2,2-trifluoroethanol (10 mL), TMSCl (0.019 mL, 0.145 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DMC). After completion, the reaction was concentrated under reduced pressure to obtain 2-((4-(6-((6-(2-Aminoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-(2-aminoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (13 mg, 14.89% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.80 - 7.65 (m, 1H), 7.34 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.44 - 4.02 (m, 4H), 3.75 - 3.78 (m, 1H), 3.44 (br s, 2 H), 3.41 - 3.37 (m, 1H), 3.29 - 3.09 (m, 1H), 2.87 - 2.74 (m, 3H), 2.74 - 2.66 (m, 4H), 2.60 - 2.52 (m, 5H), 2.30 - 2.20 (m, 2H), 1.28 - 0.97 (m, 9H); LCMS (Method F): Rt = 1.67 min, m/z = 590.3 $[M+H]^+$; HPLC (Method A): Rt = 4.57 min, 97.95%.

Example 158. 2-((4-(6-((6-(Azetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 101)

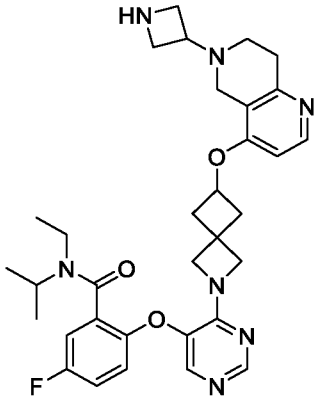


Step 1. tert-Butyl 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)azetidine-1-carboxylate



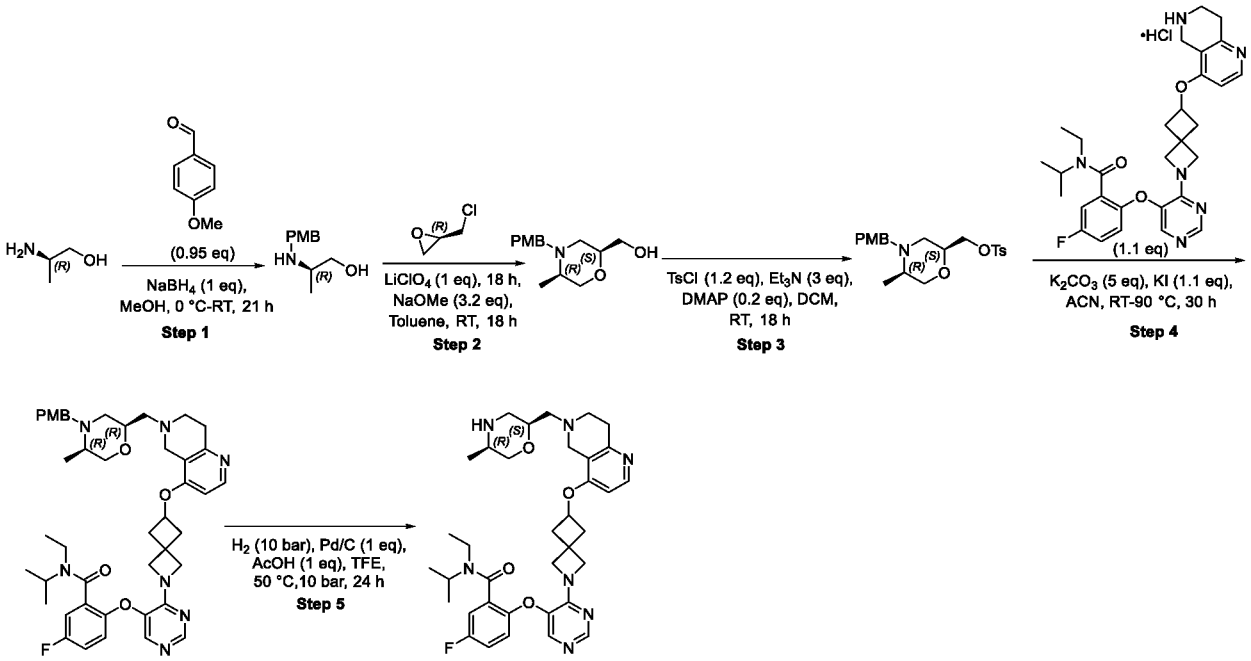
To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.16 g, 0.293 mmol) in ACN (6 mL), TEA (0.204 mL, 1.463 mmol) was added at RT. *tert*-Butyl 3-iodoazetidine-1-carboxylate (0.414 g, 1.463 mmol) was added to this reaction mixture. The reaction was stirred at 90 °C for 16 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT, quenched with water (25 mL), and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with brine (35 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *tert*-butyl 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)azetidine-1-carboxylate (0.026 g, 12.40% yield) as a solid. LCMS (Method G): Rt = 2.00 min, m/z = 702.6 $[M+H]^+$, 97.87%.

Step 2. 2-((4-(6-((6-(Azetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

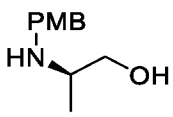


To a stirred solution of *tert*-butyl 3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)azetidine-1-carboxylate (0.026 g, 0.037 mmol) in 2,2,2-trifluoroethanol (10 mL), TMSCl (0.019 mL, 0.148 mmol) was added dropwise at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-(azetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.02 g, 87% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 - 8.25 (m, 1H), 8.21 - 8.17 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.70 - 6.65 (m, 1H), 4.80 - 4.68 (m, 1H), 4.48 - 4.05 (m, 4H), 3.92 - 3.67 (m, 2H), 3.62 - 3.35 (m, 4H), 3.31 - 3.09 (m, 5H), 2.85 - 2.73 (m, 4H), 2.63 - 2.55 (m, 2H), 2.31 - 2.22 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.39 min, m/z = 602.4 $[M+H]^+$, 98.75%; HPLC (Method F): Rt = 4.58 min, 97.39%.

Example 159. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2*S*,5*R*)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 267)

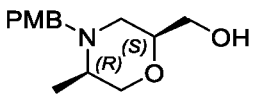


Step 1. (R)-2-((4-Methoxybenzyl)amino)Propan-1-ol



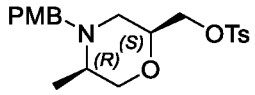
In a 250 mL two neck round bottom flask under a nitrogen atmosphere, (*R*)-2-aminopropan-1-ol (3 g, 39.9 mmol) was added in methanol (40 mL). To this solution, 4-methoxybenzaldehyde (5.17 g, 37.9 mmol) was added, and the reaction was stirred at RT for 3 h. To this reaction mixture, sodium borohydride (1.511 g, 39.9 mmol) was added portion-wise at 0 °C, and the reaction was stirred at RT for 18 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (50 mL), and the MeOH solvent was removed under reduced pressure. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layer was washed with water (2 x 50 mL) dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude (*R*)-2-((4-methoxybenzyl)amino)propan-1-ol (6.2 g, 78% yield) as a viscous liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23 (d, J = 8.6 Hz, 2H), 6.89 - 6.83 (m, 2H), 4.48 (br t, J = 5.3 Hz, 1H), 3.73 (s, 3H), 3.71 - 3.54 (m, 2H), 3.31 - 3.19 (m, 2H), 2.14 - 2.05 (m, 1H), 1.85 (br s, 1H), 0.93 (d, J = 6.4 Hz, 3H); LCMS (Method G): Rt = 1.24 min, m/z = 196.3 $[M+H]^+$, 98.63%.

Step 2. ((2S,5R)-4-(4-Methoxybenzyl)-5-Methylmorpholin-2-yl)methanol



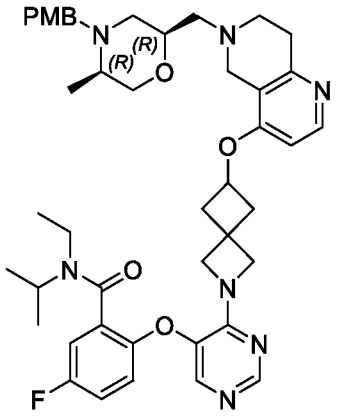
In a 100 mL two neck round bottom flask under a nitrogen atmosphere, (*R*)-2-((4-methoxybenzyl)amino)propan-1-ol (3.1 g, 15.88 mmol) was added in toluene (50 mL). To this solution, (*R*)-2-(chloromethyl)oxirane (1.469 g, 15.88 mmol) and lithium perchlorate (1.689 g, 15.88 mmol) were added at RT, and the reaction was stirred at RT for 18 h. To this reaction mixture, sodium methoxide (10.98 mL, 50.8 mmol) was added, and the reaction was stirred at RT for 18 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layer was washed with water (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to afford ((2*S*,5*R*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methanol (1.25 g, 31.3% yield) as a viscous liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.61 - 4.55 (m, 1H), 3.73 (s, 3H), 3.63 - 3.48 (m, 2H), 3.48 - 3.35 (m, 4H), 3.30 - 3.19 (m, 1H), 2.75 - 2.64 (m, 1H), 2.40 - 2.32 (m, 1H), 2.31 - 2.21 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H); LCMS (Method G): Rt = 1.58 min, m/z = 252.1 $[M+H]^+$, 89.26%.

Step 3. ((2S,5R)-4-(4-Methoxybenzyl)-5-methylmorpholin-2-yl)methyl 4-methylbenzenesulfonate



In a 50 mL two neck round bottom flask under a nitrogen atmosphere, ((2*S*,5*R*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methanol (360 mg, 1.432 mmol) was added in DCM (3 mL). Et_3N (0.599 mL, 4.30 mmol) and DMAP (35.0 mg, 0.286 mmol) were added to this solution at RT. To this reaction mixture, *p*-TsCl (328 mg, 1.719 mmol) was added at RT, and the reaction was stirred at the same temperature for 18 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. To this residue, water (30 mL) was added and the mixture was extracted with hexane (3 x 30 mL). The combined organic layer was washed with aq. $NaHCO_3$ (2 x 25 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude ((2*S*,5*R*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl 4-methylbenzenesulfonate (0.4 g, 68.5% yield) as a viscous liquid. LCMS (Method B): Rt = 1.88 min, m/z = 406.3 $[M+H]^+$, 99.51%.

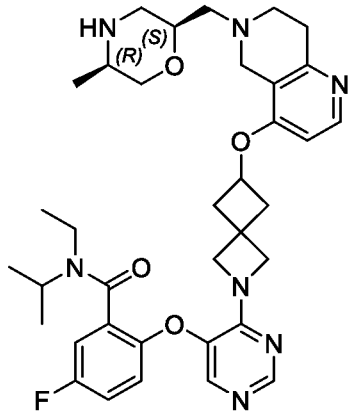
Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-(((6-(((2R,5R)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (500 mg, 0.857 mmol) in acetonitrile (10 mL), powdered K_2CO_3 (593 mg, 4.29 mmol)) and KI (157 mg, 0.943 mmol) were added at RT under a nitrogen atmosphere. To this reaction mixture, ((2*S*,5*R*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl 4-methylbenzenesulfonate (382 mg, 0.943 mmol) was added at RT, and the reaction was stirred at 90 °C for 30 h. The progress of the reaction was monitored by TLC (8% MeOH in DCM).

After completion, the reaction was quenched with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with water (2 x 50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2R,5R)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (250 mg,, 35.0% yield) as a solid. LCMS (Method G): Rt = 2.21 min, m/z = 780.7 $[M+H]^+$, 93.73%.

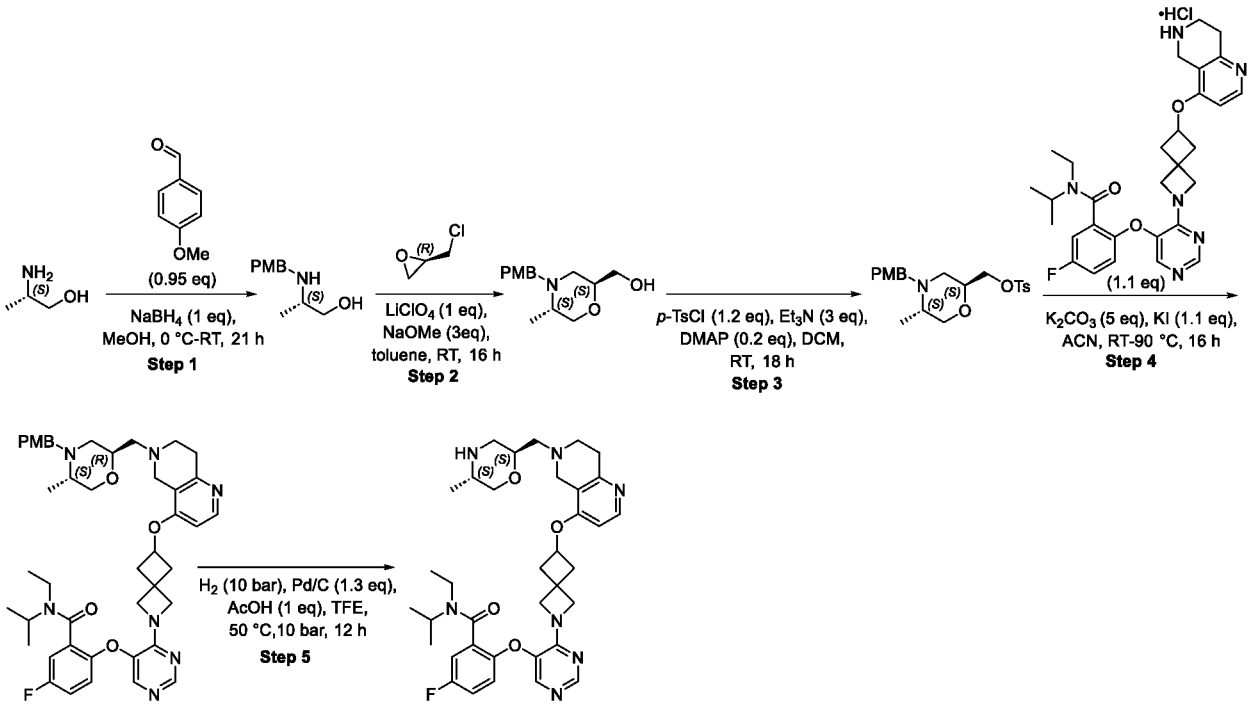
Step 5. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(((2S,5R)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



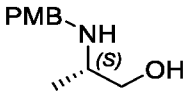
In a stainless steel tiny clave, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2R,5R)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (200 mg, 0.256 mmol) was added in TFE (0.2 mL). To this solution, AcOH (15.40 mg, 0.256 mmol) and Pd-C (273 mg, 0.256 mmol) were added, and the reaction was stirred at 50 °C under a hydrogen gas atmosphere (at 10 bar pressure) for 24 h. The progress of the reaction was monitored by TLC (15% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 10 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2S,5R)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (55 mg, 32.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.18 (br d, *J* = 5.6 Hz, 1H), 7.80 - 7.64 (m, 1H), 7.37 - 7.20 (m, 2H), 7.12 - 6.97 (m, 1H), 6.71 - 6.61 (m, 1H), 4.83 - 4.69 (m, 1H), 4.34 - 4.06 (m,

4H), 3.81 - 3.68 (m, 1H), 3.68 - 3.59 (m, 1H), 3.56 - 3.34 (m, 5H), 3.28 - 3.09 (m, 2H), 2.83 - 2.73 (m, 6H), 2.73 - 2.63 (m, 5H), 2.32 - 2.21 (m, 2H), 1.31 - 0.95 (m, 12H); LCMS (Method G): Rt = 1.69 min, m/z = 660.6 $[M+H]^+$; HPLC (Method A): Rt = 4.76 min, 99.68%; Chiral SFC (Method AR): Rt = 6.40 min, 91.81%.

Example 160. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2S,5S)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 272)



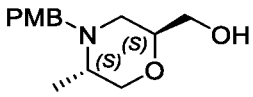
Step 1. (S)-2-((4-Methoxybenzyl)amino)Propan-1-ol



This compound was synthesized following the procedure described for the synthesis of Example 159, step 1, starting with 1 equivalent of (*S*)-2-aminopropan-1-ol, to afford (*S*)-2-((4-methoxybenzyl)amino)propan-1-ol as a viscous liquid.

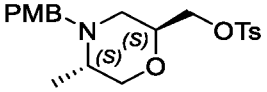
Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 - 7.24 (m, 2H), 6.92 - 6.82 (m, 2H), 3.86 - 3.80 (m, 5H), 3.74 - 3.67 (m, 1H), 3.62 (dd, *J* = 4.1, 10.6 Hz, 1H), 3.29 (dd, *J* = 7.0, 10.5 Hz, 1H), 2.92 - 2.80 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 3H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.21 min, m/z = 196.1 $[M+H]^+$, 99.50%.

Step 2. ((2S,5S)-4-(4-Methoxybenzyl)-5-Methylmorpholin-2-yl)methanol



This compound was synthesized following the procedure described for the synthesis of Example 159, step 2, starting with (*S*)-2-((4-methoxybenzyl)amino)propan-1-ol, except that 3.0 equivalents of NaOMe was used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to afford ((2*S*,5*S*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methanol as a viscous liquid. Yield: 48.1%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 - 7.21 (m, 2H), 6.90 - 6.85 (m, 2H), 4.12 - 4.07 (m, 1H), 3.83 (s, 3H), 3.82 - 3.77 (m, 1H), 3.65 - 3.53 (m, 2H), 3.53 - 3.45 (m, 1H), 3.36 (dd, *J* = 10.4, 11.2 Hz, 1H), 3.03 (d, *J* = 13.0 Hz, 1H), 2.59 (dd, *J* = 2.2, 11.5 Hz, 1H), 2.45 - 2.34 (m, 1H), 1.93 (dd, *J* = 10.3, 11.5 Hz, 2H), 1.11 (d, *J* = 6.2 Hz, 3H); LCMS (Method G): Rt = 1.53 min, m/z = 252.2 $[M+H]^+$, 99.31%.

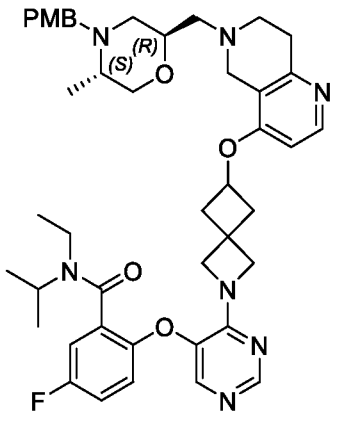
Step 3. ((2S,5S)-4-(4-Methoxybenzyl)-5-Methylmorpholin-2-yl)methyl 4-methylbenzenesulfonate



This compound was synthesized following the procedure described for the synthesis of Example 159, step 3, starting with ((2*S*,5*S*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methanol, to afford crude ((2*S*,5*S*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl 4-methylbenzenesulfonate as a viscous liquid.

Yield: 73.3%; LCMS (Method G): Rt = 2.28 min, m/z = 406.2 $[M+H]^+$, 98.29%.

Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-(((6-((((2R,5S)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

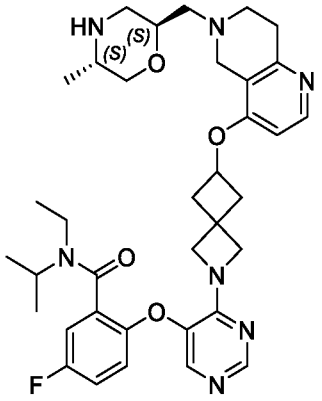


This compound was synthesized following the procedure described for the synthesis of Example 159, step 4, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1 equivalent of ((2*S*,5*S*)-4-(4-methoxybenzyl)-

5-methylmorpholin-2-yl)methyl 4-methylbenzenesulfonate was used, to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2*R*,5*S*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 29.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.11 - 7.00 (m, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.68 - 6.63 (m, 1H), 4.78 - 4.65 (m, 1H), 4.31 - 4.08 (m, 4H), 4.01 - 3.92 (m, 1H), 3.82 - 3.65 (m, 5H), 3.63 - 3.55 (m, 1H), 3.46 - 3.35 (m, 3H), 3.29 - 3.10 (m, 2H), 3.06 - 2.99 (m, 1H), 2.82 - 2.59 (m, 7H), 2.46 - 2.38 (m, 2H), 2.30 - 2.18 (m, 3H), 1.82 - 1.72 (m, 1H), 1.25 - 0.94 (m, 12H); LCMS (Method B): Rt = 1.29 min, m/z = 780.0 $[M+H]^+$, 93.20%.

Step 5. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(((2S,5S)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

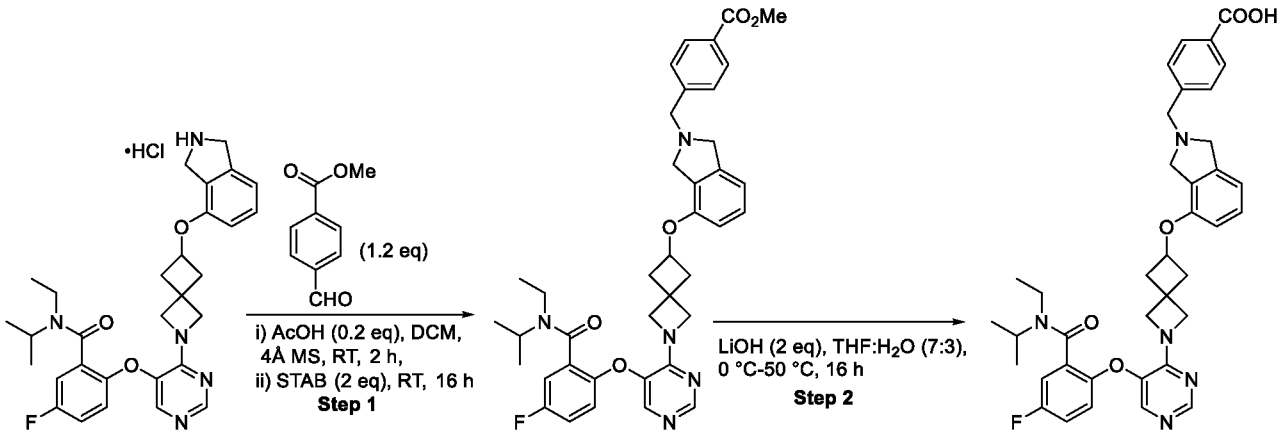


This compound was synthesized following the procedure described for the synthesis of Example 159, step 5, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2*R*,5*S*)-4-(4-methoxybenzyl)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 1.3 equivalents of Pd/C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2*S*,5*S*)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

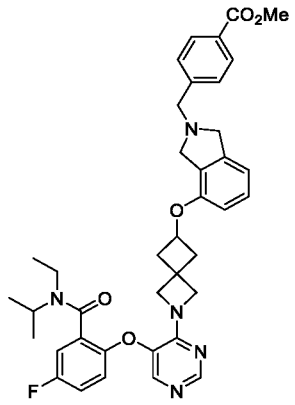
Yield: 17.45%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 - 8.15 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.12 - 6.99 (m, 1H), 6.71 - 6.62 (m, 1H), 4.80 - 4.70 (m, 1H), 4.36 - 4.05 (m, 4H), 3.76 (spt, J = 6.6 Hz, 1H), 3.69 - 3.62 (m, 1H), 3.54 - 3.48 (m,

1H), 3.46 (s, 2H), 3.44 - 3.36 (m, 1H), 3.28 - 3.13 (m, 2H), 2.99 (t, *J* = 10.5 Hz, 1H), 2.85 (dd, *J* = 2.3, 12.3 Hz, 1H), 2.81 - 2.75 (m, 4H), 2.72 - 2.63 (m, 2H), 2.49 - 2.38 (m, 3H), 2.30 - 2.22 (m, 2H), 1.29 - 0.96 (m, 9H), 0.85 (d, *J* = 6.0 Hz, 3H), one proton is merging with moisture peak; LCMS (Method G): Rt = 1.72 min, m/z = 660.6 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 99.87%; SFC (Method U): Rt = 6.68 min, 97.47%.

Example 161. 4-((4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoic acid (Compound No. 31)



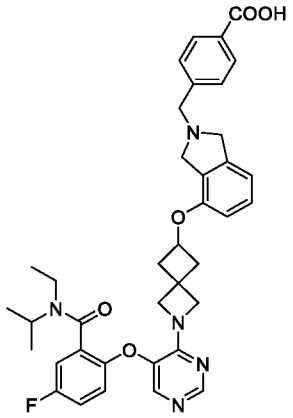
Step 1. Methyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoate



In a dried, 50 mL two neck round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride (200 mg, 0.352 mmol) was added in DCM (10 mL). To this solution, methyl 4-formylbenzoate (69.4 mg, 0.422 mmol), molecular sieves (4Å) (~100 mg), and AcOH (4.03 µL, 0.070 mmol) were added at RT. The reaction was stirred at RT for 2 h. To this reaction mixture, sodium triacetoxyborohydride (149 mg, 0.704 mmol) was added at RT, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was diluted with water (10 mL) and

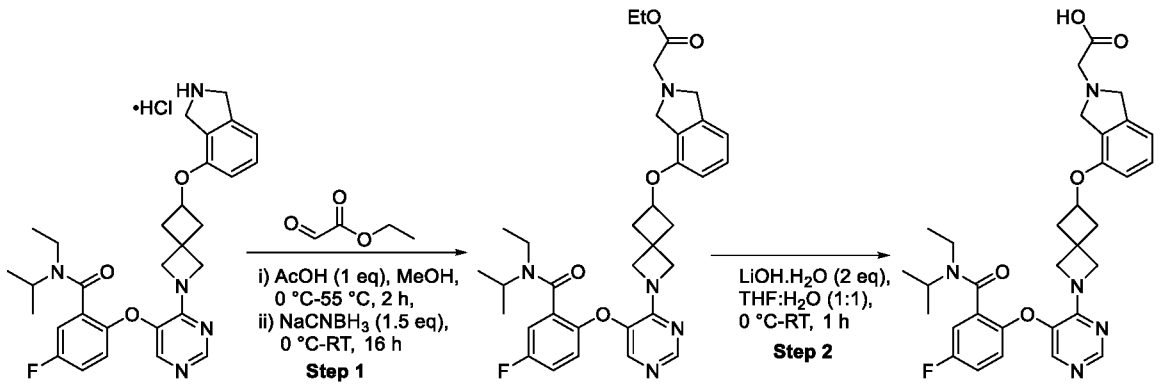
extracted with 10% MeOH in DCM (2 x 25 mL). The combined organic layer was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80-85% EtOAc in hexane) to obtain methyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoate (150 mg, 52.0% yield) as an oil. LCMS (Method B): Rt = 1.86 min, m/z = 680.4 $[M+H]^+$; 82.97%.

Step 2. 4-((4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoic acid

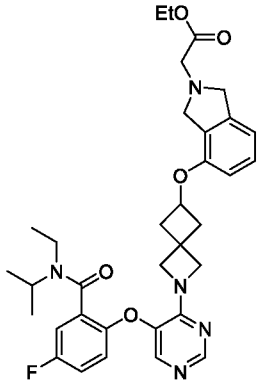


In a dried, 10 mL two neck round bottom flask, methyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoate (140 mg, 0.206 mmol) was added in THF (1 mL). To this solution, LiOH (9.86 mg, 0.412 mmol) in water (0.4 mL) was added at 0 °C. The reaction was stirred at 50 °C for 16 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure, cooled to 0 °C, and acidified with 1.5 N HCl (5 mL). The precipitate was filtered, and the solid was dried under a vacuum. The crude was purified by Prep HPLC (Method AC) to obtain 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)benzoic acid (137 mg, 49.3% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85 (s, 1H), 8.30 - 8.25 (m, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.76 - 7.63 (m, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.34 - 7.21 (m, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.09 - 6.99 (m, 1H), 6.81 (d, J = 7.4 Hz, 1H), 6.66 - 6.62 (m, 1H), 4.70 - 4.60 (m, 1H), 4.46 - 4.06 (m, 4H), 3.93 (s, 2H), 3.87 (s, 2H), 3.77 (s, 2H), 3.75 - 3.67 (m, 1H), 3.44 - 3.37 (m, 1H), 3.26 - 3.05 (m, 1H), 2.76 - 2.69 (m, 2H), 2.24 - 2.15 (m, 2H), 1.22 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.43 min, m/z = 666.3 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 99.66 %.

Example 162. 2-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetic acid (Compound No. 32)



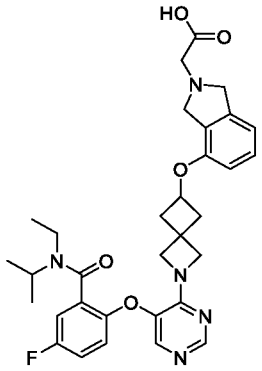
Step 1. Ethyl 2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetate



This compound was synthesized following the procedure described for the synthesis of Example 161, step 1, starting with *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride, except that 1 equivalent of ethyl 2-oxoacetate, 1.5 equivalents of $NaCNBH_3$, and 1 equivalent of AcOH were used in MeOH as the solvent. The imine formation reaction was stirred at 55 °C. After completion, ice-cold water was added to the reaction and the mixture was extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80% EtOAc in hexane) to afford ethyl 2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetate as a solid.

Yield: 22.98%; LCMS (Method B): Rt = 1.81 min, m/z = 618.6 $[M+H]^+$; 89.00%.

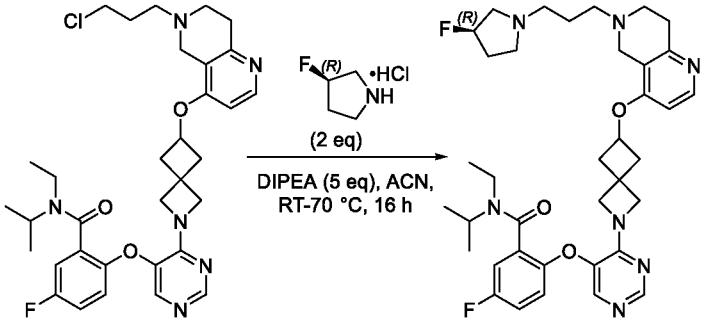
Step 2. 2-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetic acid



This compound was synthesized following the procedure described for the synthesis of Example 161, step 2, starting with ethyl 2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetate. 1:1 THF/H_2O was used as the solvent, and the reaction was stirred in a pressure vial. The reaction was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc. The aqueous layer was acidified with 1N HCl and extracted with 10% MeOH in DCM. The combined organic layer dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method Y) to obtain 2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)acetic acid as a solid.

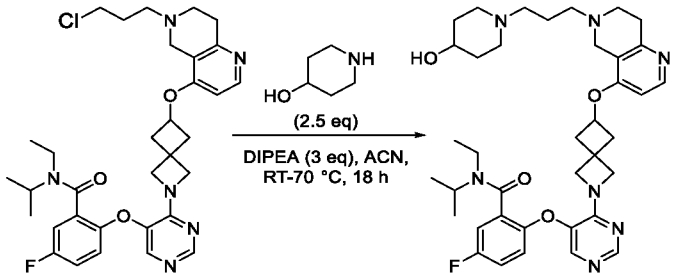
Yield: 21.79%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.24 (m, 1H), 7.76 - 7.63 (m, 1H), 7.33 - 7.22 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.10 - 7.01 (m, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 4.71 - 4.60 (m, 1H), 4.46 - 4.08 (m, 4H), 4.06 (br s, 2H), 4.00 (br s, 2H), 3.80 - 3.71 (m, 1H), 3.49 (br s, 2H), 2.77 - 2.71 (m, 2H), 2.28 - 2.17 (m, 2H), 1.22 - 0.97 (m, 9H), three protons merged with solvent peaks; LCMS (Method D): Rt = 1.44 min, m/z = 590.5 $[M+H]^+$; HPLC (Method A): Rt = 4.46 min, 99.30%.

Example 163. (*R*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 156)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of (*R*)-3-fluoropyrrolidine hydrochloride was used. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*R*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 49.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.70 - 6.63 (m, 1H), 5.31 - 5.08 (m, 1H), 4.79 - 4.69 (m, 1H), 4.35 - 4.07 (m, 4H), 3.80-3.71 (m, 1H), 3.42 (s, 2H), 3.40 - 3.37 (m, 1H), 3.26 - 3.11 (m, 2H), 2.85 - 2.73 (m, 6H), 2.72 - 2.65 (m, 2H), 2.46 - 2.38 (m, 4H), 2.31 - 2.22 (m, 3H), 2.21 - 2.01 (m, 1H), 1.94 - 1.78 (m, 1H), 1.75 - 1.62 (m, 2H), 1.25 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.39 min, m/z = 676.4 $[M+H]^+$; HPLC (Method A): Rt = 5.29 min, 97.29%; Chiral SFC (Method AP): Rt = 0.78 min, 100%.

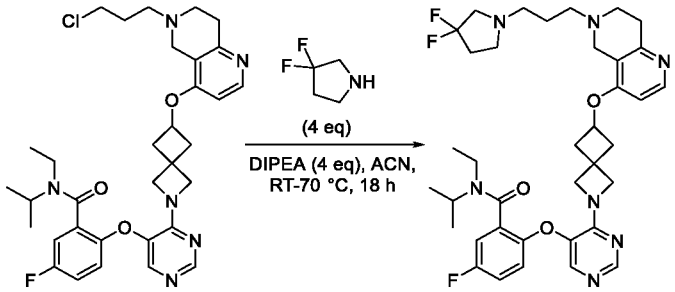
Example 164. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(4-hydroxypiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 123)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of DIPEA and 2.5 equivalents of piperidin-4-ol were used. The reaction was stirred at 70 °C. The crude was purified by Prep HPLC (Method AG) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(4-hydroxypiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 48.3%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.36 - 7.19 (m, 2H), 7.13 - 6.93 (m, 1H), 6.73 - 6.59 (m, 1H), 4.80 - 4.68 (m, 1H), 4.60 - 4.47 (m, 1H), 4.31 - 4.05 (m, 4H), 3.75 (quin, J = 6.4 Hz, 1H), 3.51 - 3.38 (m, 3H), 3.23 - 3.11 (m, 2H), 2.83 - 2.60 (m, 7H), 2.55 - 2.52 (m, 1H), 2.48 - 2.45 (m, 2H), 2.32 - 2.22 (m, 4H), 1.98 (br t, J = 10.1 Hz, 2H), 1.76 - 1.59 (m, 4H), 1.43 - 1.32 (m, 2H), 1.24 - 0.96 (m, 9H); LCMS (Method A): Rt = 2.04 min, m/z = 688.3 $[M+H]^+$; HPLC (Method A): Rt = 4.74 min, 98.88%.

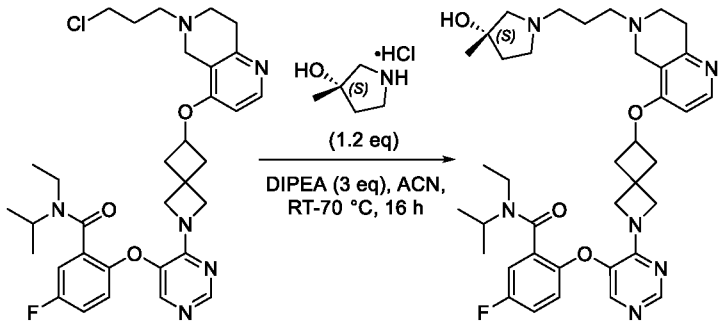
Example 165. 2-((4-(6-((6-(3-(3,3-Difluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 175)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, staring with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 4 equivalents of DIPEA and 4 equivalents of 3,3-difluoropyrrolidine were used. The reaction was stirred at 70 °C. The crude was purified by Prep HPLC (Method B) to afford 2-((4-(6-((6-(3-(3,3-difluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

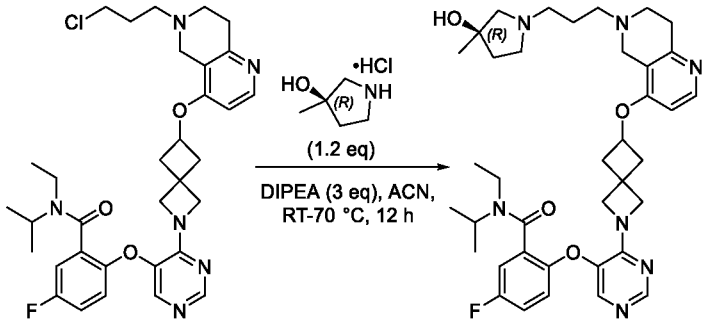
Yield: 20.30%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.79 - 7.63 (m, 1H), 7.35 - 7.20 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.64 (m, 1H), 4.85 - 4.67 (m, 1H), 4.35 - 4.05 (m, 4H), 3.81 - 3.71 (m, 1H), 3.41 (s, 2H), 3.38 - 3.35 (m, 1H), 3.28 - 3.10 (m, 2H), 2.91 - 2.73 (m, 6H), 2.72 - 2.63 (m, 5H), 2.46 - 2.41 (m, 2H), 2.31 - 2.14 (m, 4H), 1.66 (quin, J = 7.3 Hz, 2H), 1.30 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.94 min, m/z = 694.7 $[M+H]^+$; HPLC (Method A): Rt = 5.60 min, 99.79%.

Example 166. (*S*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 157)



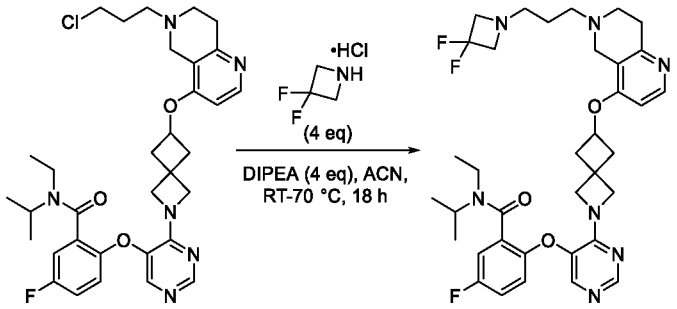
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of DIPEA and 1.2 equivalents of (*S*)-3-methylpyrrolidin-3-ol hydrochloride were used. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (S)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 30.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.15 (m, 1H), 7.79 - 7.64 (m, 1H), 7.35 - 7.19 (m, 2H), 7.12 - 6.96 (m, 1H), 6.71 - 6.60 (m, 1H), 6.33 - 6.33 (m, 1H), 4.80 - 4.67 (m, 1H), 4.52 - 4.47 (m, 1H), 4.34 - 4.05 (m, 4H), 3.75 (sep, *J* = 6.6 Hz, 1H), 3.45 - 3.34 (m, 3H), 3.28 - 3.10 (m, 2H), 2.84 - 2.77 (m, 4H), 2.71 - 2.55 (m, 2H), 2.45 - 2.35 (m, 6H), 2.31 - 2.22 (m, 2H), 1.81 - 1.54 (m, 4H), 1.23 (s, 3H), 1.21 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.31 min, m/z = 688.2 $[M+H]^+$; HPLC (Method A): Rt = 4.73 min, 97.5%; Chiral SFC (Method K): Rt = 5.89 min, 98.56%.

Example 167. (*R*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 158)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of DIPEA and 1.2 equivalents of (*R*)-3-methylpyrrolidin-3-ol hydrochloride were used. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*R*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 35.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.77 - 7.63 (m, 1H), 7.34 - 7.19 (m, 2H), 7.11 - 7.00 (m, 1H), 6.70 - 6.64 (m, 1H), 4.78 - 4.67 (m, 1H), 4.34 - 4.04 (m, 4H), 3.80 - 3.71 (m, 1H), 3.44 - 3.37 (m, 3H), 3.28 - 3.11 (m, 2H), 2.86 - 2.73 (m, 4H), 2.72 - 2.64 (m, 3H), 2.62 - 2.54 (m, 1H), 2.48 - 2.44 (m, 1H), 2.42 (s, 2H), 2.41 - 2.31 (m, 3H), 2.30 - 2.22 (m, 2H), 1.78 - 1.58 (m, 4H), 1.27 - 1.22 (m, 3H), 1.21 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.75 min, m/z = 688.3 $[M+H]^+$; HPLC (Method A): Rt = 4.74 min, 98.43%; Chiral SFC (Method K): Rt = 5.72 min, 100%.

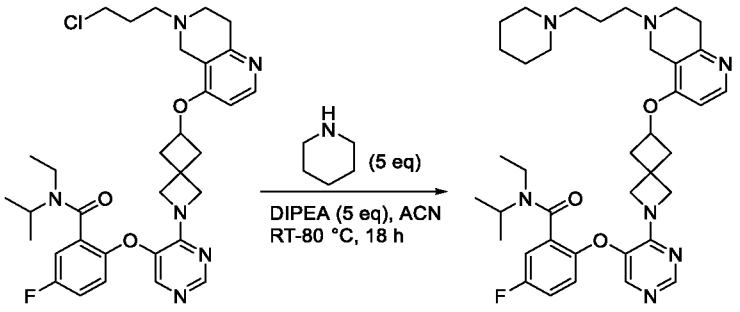
Example 168. 2-((4-(6-((6-(3-(3,3-Difluoroazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 170)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 4 equivalents of DIPEA and 4 equivalents of 3,3-difluoroazetidine hydrochloride were used. The reaction was stirred at 70 °C. The crude was purified by Prep HPLC (Method AI) to afford 2-((4-(6-((6-(3-(3,3-difluoroazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 19.65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.79 - 7.65 (m, 1H), 7.37 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.72 - 6.61 (m, 1H), 4.81 - 4.70 (m, 1H), 4.32 - 4.07 (m, 4H), 3.76 (sep, J = 6.7 Hz, 1H), 3.54 (t, J = 12.5 Hz, 4H), 3.44 - 3.34 (m, 3H), 3.28 - 3.07 (m, 2H), 2.84 - 2.75 (m, 4H), 2.70 - 2.62 (m, 3H), 2.57 - 2.54 (m, 2H), 2.29 - 2.21 (m, 2H), 1.55 (quin, J = 7.0 Hz, 2H), 1.31 - 0.90 (m, 9H); LCMS (Method A): Rt = 2.42 min, m/z = 680.4 $[M+H]^+$; HPLC (Method A): Rt = 5.43 min, 99.72%.

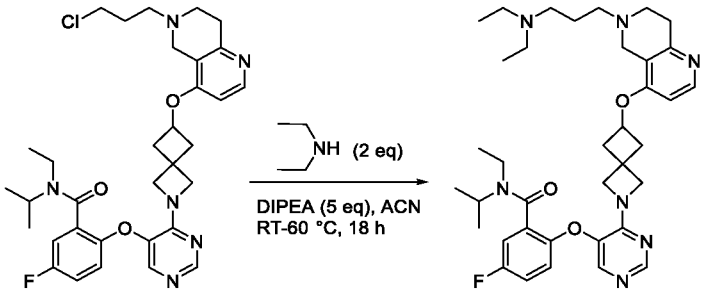
Example 169. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(piperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 99)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 5 equivalents of piperidine was used. The reaction was stirred at 80 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(piperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

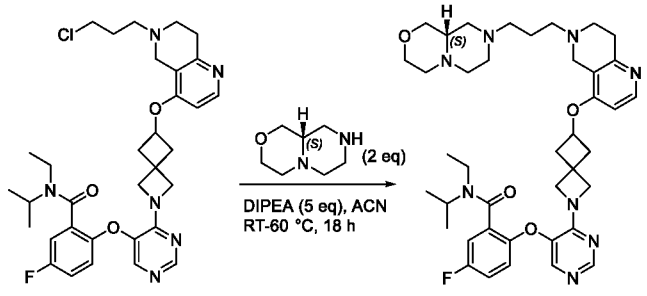
Yield: 12.06%.; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.23 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.63 (m, 1H), 4.79 - 4.69 (m, 1H), 4.45 - 4.08 (m, 4H), 3.80 - 3.70 (m, 1H), 3.53 - 3.36 (m, 5H), 3.27 - 3.12 (m, 2H), 2.83 - 2.67 (m, 6H), 2.30 - 2.21 (m, 4H), 1.72 - 1.60 (m, 2H), 1.53 - 1.45 (m, 4H), 1.42 - 1.37 (m, 2H), 1.24 - 0.97 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.90 min, m/z = 672.4 $[M+H]^+$; HPLC (Method A): Rt = 5.26 min, 97.10%.

Example 170. 2-((4-(6-((6-(3-(Diethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 100)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of diethylamine was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((4-(6-((6-(3-(diethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide. Yield: 27.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.62 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.68 - 6.63 (m, 1H), 4.80 - 4.69 (m, 1H), 4.47 - 4.09 (m, 4H), 3.80 - 3.70 (m, 1H), 3.44 - 3.35 (m, 4H), 3.28 - 3.14 (m, 2H), 2.83 - 2.74 (m, 4H), 2.70 - 2.67 (m, 2H), 2.47 - 2.42 (m, 6H), 2.30 - 2.21 (m, 2H), 1.66 - 1.56 (m, 2H), 1.22 - 0.98 (m, 9H), 0.94 (br t, J = 6.9 Hz, 6H); LCMS (Method G): Rt = 1.74 min, m/z = 660.7 $[M+H]^+$; HPLC (Method A): Rt = 5.19 min, 96.88%.

Example 171. (*S*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 109)

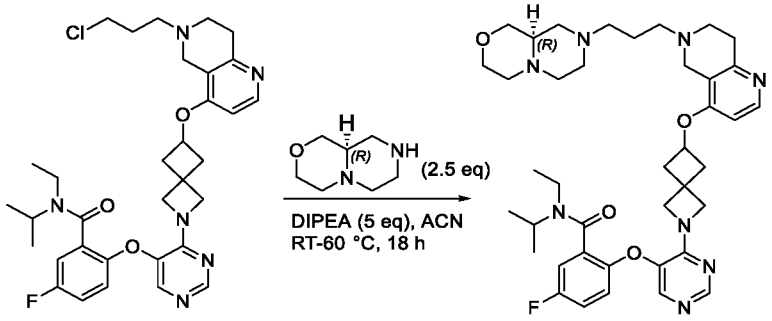


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of (*S*)-octahydropyrazino[2,1-c][1,4]oxazine

was used. The reaction was concentrated under reduced pressure. The crude product was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*S*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 20.47%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.80 - 3.69 (m, 2H), 3.59 (dd, *J* = 2.8, 10.8 Hz, 1H), 3.47 (dt, *J* = 2.3, 11.3 Hz, 1H), 3.43 - 3.36 (m, 3H), 3.27 - 3.12 (m, 2H), 3.06 (t, *J* = 10.6 Hz, 1H), 2.85 - 2.72 (m, 5H), 2.70 - 2.56 (m, 6H), 2.31 - 2.22 (m, 4H), 2.21 - 2.00 (m, 4H), 1.69 - 1.53 (m, 3H), 1.22 - 0.97 (m, 9H); LCMS (Method C): Rt = 1.63 min, m/z = 729.5 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 99.15%. Chiral SFC (Method D): Rt = 2.23 min, 98.08%.

Example 172. (*R*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 108)

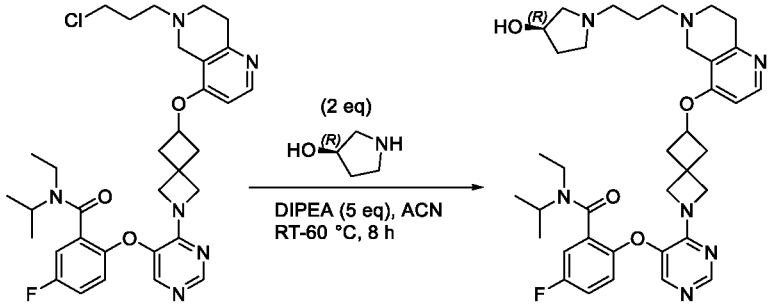


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2.5 equivalents of (*R*)-octahydropyrazino[2,1-c][1,4]oxazine was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*R*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(hexahydropyrazino[2,1-

c][1,4]oxazin-8(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 27.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.79 - 3.69 (m, 2H), 3.59 (dd, J = 2.6, 10.8 Hz, 1H), 3.47 (dt, J = 2.3, 11.4 Hz, 1H), 3.43 - 3.37 (m, 3H), 3.28 - 3.13 (m, 2H), 3.06 (t, J = 10.6 Hz, 1H), 2.83 - 2.74 (m, 5H), 2.70 - 2.56 (m, 6H), 2.32 - 2.22 (m, 4H), 2.21 - 1.99 (m, 4H), 1.68 - 1.52 (m, 3H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.66 min, m/z = 729.7 $[M+H]^+$; HPLC (Method A): Rt = 4.71 min, 96.80%. Chiral SFC (Method E): Rt = 1.84 min, 99.26%.

Example 173. (*R*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxypyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 117)

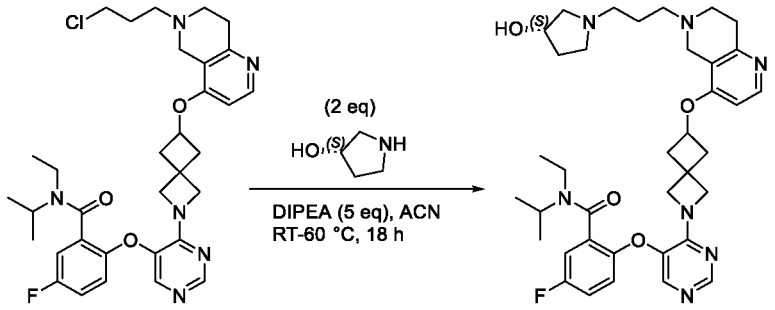


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of (*R*)-pyrrolidin-3-ol was used, and the reaction was stirred in a pressure vial. The reaction was diluted with water and extracted with DCM. The combined organic layer was washed with brine solution, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under the reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*R*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxypyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 70.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.75 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.64 (m, 1H), 4.78 - 4.69 (m, 1H), 4.64 (d, J = 4.5 Hz, 1H), 4.46 - 4.08 (m, 5H), 3.82 - 3.70 (m, 1H), 3.45 - 3.37 (m, 3H), 3.28 - 3.10 (m, 2H), 2.83 - 2.74 (m, 4H), 2.67 - 2.63 (m, 2H), 2.42 - 2.35 (m, 3H), 2.30 -

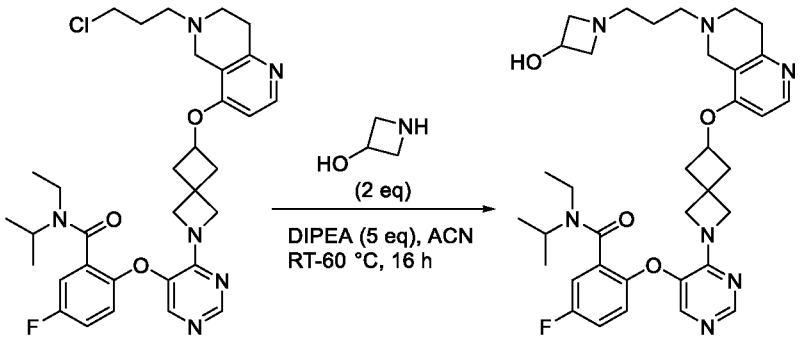
2.22 (m, 3H), 2.01 - 1.90 (m, 1H), 1.64 (quin, *J* = 7.1 Hz, 2H), 1.56 - 1.47 (m, 1H), 1.22 - 0.97 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.52 min, m/z = 674.6 $[M+H]^+$; HPLC (Method A): Rt = 4.78 min, 98.19%; Chiral SFC (Method K): Rt = 5.15 min, 99.52%.

Example 174. (*S*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxypyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 126)



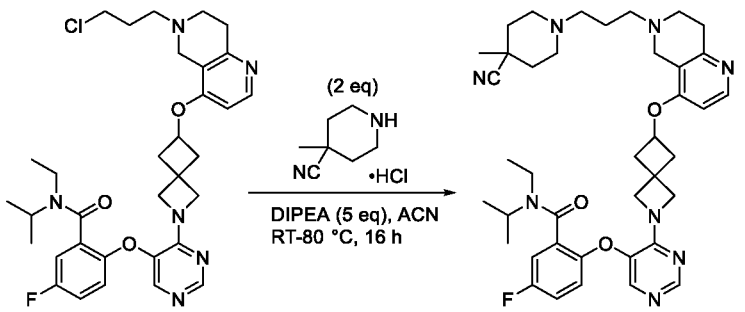
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of (*S*)-pyrrolidin-3-ol was used, and the reaction was stirred in a pressure vial. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*S*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxypyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.
Yield: 75%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.75 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.64 (m, 1H), 4.78 - 4.69 (m, 1H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.46 - 4.08 (m, 5H), 3.82 - 3.70 (m, 1H), 3.45 - 3.37 (m, 3H), 3.28 - 3.10 (m, 2H), 2.83 - 2.74 (m, 4H), 2.67 - 2.63 (m, 2H), 2.42 - 2.35 (m, 3H), 2.30 - 2.22 (m, 3H), 2.01 - 1.90 (m, 1H), 1.64 (quin, *J* = 7.1 Hz, 2H), 1.56 - 1.47 (m, 1H), 1.22 - 0.97 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.62 min, m/z = 674.4 $[M+H]^+$; HPLC (Method A): Rt = 5.12 min, 99.23%; Chiral SFC (Method L): Rt = 0.87 min, 100%.

Example 175. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxyazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 121)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of azetidin-3-ol was used, and the reaction was stirred in a pressure vial. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxyazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 18.33%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 - 7.62 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.70 - 6.63 (m, 1H), 5.22 (d, J = 6.5 Hz, 1H), 4.80 - 4.66 (m, 1H), 4.46 - 4.06 (m, 5H), 3.80 - 3.70 (m, 1H), 3.51 - 3.46 (m, 2H), 3.43 - 3.36 (m, 3H), 3.27 - 3.12 (m, 2H), 2.82 - 2.72 (m, 4H), 2.66 - 2.60 (m, 4H), 2.48 - 2.43 (m, 3H), 2.37 (br t, J = 7.0 Hz, 2H), 2.30 - 2.21 (m, 2H), 1.48 (quin, J = 7.1 Hz, 2H), 1.24 - 0.97 (m, 9H); LCMS (Method C): Rt = 1.56 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.67 min, 97.63%.

Example 176. 2-((4-(6-((6-(3-(4-Cyano-4-methylpiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 129)

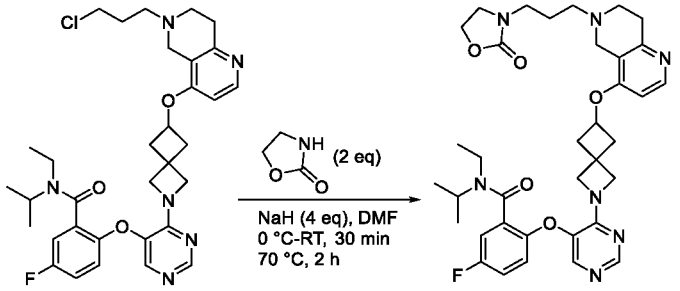


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 4-methyl piperidine-4-carbonitrile hydrochloride was used, and the reaction was stirred in a pressure vial. The reaction was stirred at 80 °C. The crude product was purified by Prep HPLC (Method T) to afford 2-((4-(6-((6-(3-(4-cyano-4-methylpiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 13.82%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.67 (m, 1H), 7.33 - 7.22 (m, 2H), 7.12 - 7.00 (m, 1H), 6.70 - 6.64 (m, 1H), 4.79 - 4.68 (m, 1H), 4.46 - 4.07 (m, 4H), 3.81 - 3.70 (m, 1H), 3.44 - 3.37 (m, 3H), 3.27 - 3.10 (m, 2H), 2.86 - 2.73 (m, 6H), 2.69 - 2.65 (m, 2H), 2.38 - 2.33 (m, 2H), 2.30 - 2.23 (m, 2H), 2.07 (t, J = 11.3 Hz, 2H), 1.83 (d, J = 12.6 Hz, 2H), 1.66 (quin, J = 7.1 Hz, 2H), 1.56 - 1.47 (m, 2H), 1.33 (s, 3H), 1.22 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.83 min, m/z = 711.5 $[M+H]^+$; HPLC (Method A): Rt = 5.72 min, 99.21%.

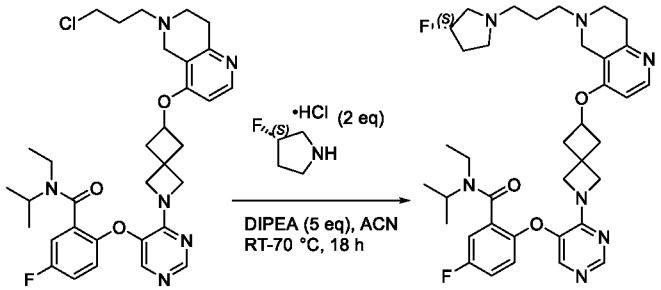
Example 177. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(2-oxooxazolidin-3-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 145)



To a stirred solution of oxazolidin-2-one (0.042 g, 0.482 mmol) in DMF (1 mL), NaH (0.039 g, 0.965 mmol) was added at 0 °C. The reaction was stirred at RT for 30 min. To this reaction, 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.150 g, 0.241 mmol) was added under a nitrogen atmosphere, and the reaction was allowed to stir at 70 °C for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was quenched with ice-cold water (10 mL) and extracted with 10% MeOH in DCM (2 x 25 mL). The crude (130 mg) was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(2-oxooxazolidin-3-

yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.044 g, 13.41% yield) as a solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.30 - 8.24 (m, 1H), 8.20 (d, *J* = 5.8 Hz, 1H), 7.82 - 7.74 (m, 1H), 7.25 - 7.18 (m, 2H), 7.02 - 6.96 (m, 1H), 6.73 (d, *J* = 5.9 Hz, 1H), 4.84 - 4.79 (m, 1H), 4.53 - 4.20 (m, 6H), 3.98 - 3.86 (m, 1H), 3.72 - 3.63 (m, 2H), 3.60 (s, 2H), 3.59 - 3.51 (m, 1H), 3.44 - 3.36 (m, 2H), 3.00 - 2.94 (m, 2H), 2.90 - 2.78 (m, 5H), 2.67 - 2.62 (m, 2H), 2.45 - 2.36 (m, 2H), 1.90 (quin, *J* = 7.2 Hz, 2H), 1.36 - 1.10 (m, 9H); LCMS (Method G): Rt = 1.58 min, m/z = 674.7 $[M+H]^+$; HPLC (Method A): Rt = 5.03 min, 99.03%.

Example 178. (*S*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 146)

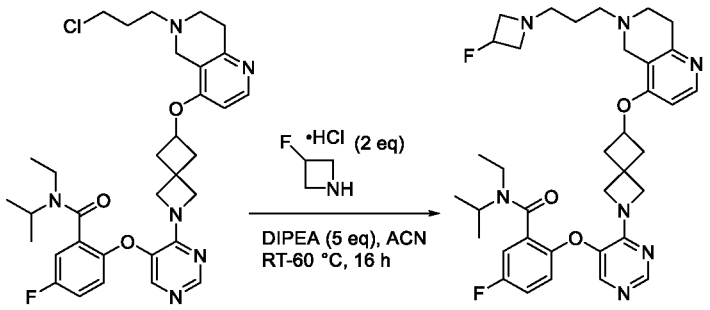


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of (*S*)-3-fluoropyrrolidine hydrochloride was used. The reaction was stirred at 70 °C. The reaction was concentrated under reduced pressure and triturated with EtOAc. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*S*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoropyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

Yield: 52.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 5.28 - 5.08 (m, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.82 - 3.70 (m, 1H), 3.42 (s, 2H), 3.40 - 3.33 (m, 1H), 3.27 - 3.11 (m, 2H), 2.85 - 2.73 (m, 6H), 2.71 - 2.67 (m, 2H), 2.64 - 2.57 (m, 1H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.32 - 2.22 (m, 3H), 2.20 - 2.03 (m, 1H), 1.93 - 1.77 (m, 1H), 1.67 (quin, *J* = 7.2 Hz, 2H), 1.22 - 0.98 (m, 9H), one proton merged with solvent peak;

LCMS (Method G): Rt = 1.88 min, m/z = 676.7 $[M+H]^+$; HPLC (Method A): R t = 5.26 min, 99.27%; Chiral SFC (Method M): Rt = 2.53 min, 100%.

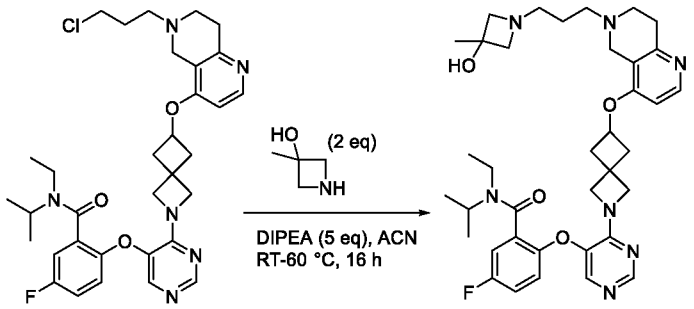
Example 179. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoroazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 163)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 3-fluoroazetidine hydrochloride was used, and the reaction was stirred in a pressure vial. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-fluoroazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 28.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.19 - 8.16 (m, 1H), 7.76 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 6.98 (m, 1H), 6.68 - 6.64 (m, 1H), 5.23 - 5.02 (m, 1H), 4.79 - 4.69 (m, 1H), 4.47 - 4.07 (m, 4H), 3.81 - 3.69 (m, 1H), 3.60 - 3.48 (m, 2H), 3.43 - 3.37 (m, 3H), 3.27 - 3.12 (m, 2H), 3.07 - 2.96 (m, 2H), 2.82 - 2.75 (m, 4H), 2.67 - 2.63 (m, 2H), 2.48 - 2.43 (m, 3H), 2.31 - 2.22 (m, 2H), 1.51 (quin, J = 7.1 Hz, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.28 min, m/z = 662.2 $[M+H]^+$; HPLC (Method A): Rt = 5.19 min, 99.88%.

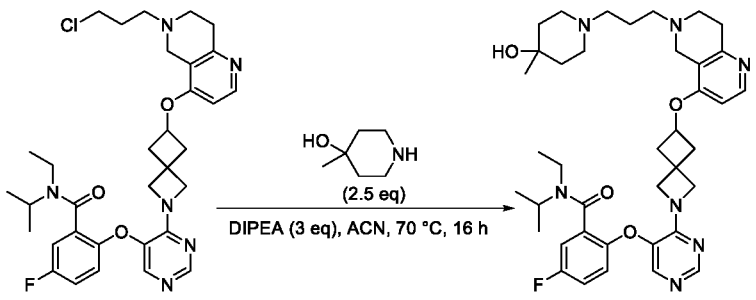
Example 180. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 168)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 3-methylazetidin-3-ol was used, and the reaction was stirred in a pressure vial. The reaction was diluted with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide.

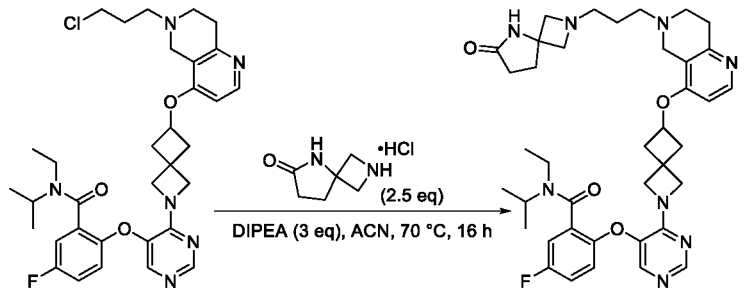
Yield: 21.87%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.65 (m, 1H), 5.06 (s, 1H), 4.80 - 4.70 (m, 1H), 4.47 - 4.07 (m, 4H), 3.80 - 3.71 (m, 1H), 3.45 - 3.36 (m, 3H), 3.27 - 3.21 (m, 1H), 3.18 - 3.14 (m, 2H), 2.84 - 2.73 (m, 6H), 2.67 - 2.63 (m, 2H), 2.47 - 2.44 (m, 2H), 2.40 (t, J = 7.0 Hz, 2H), 2.31 - 2.22 (m, 2H), 1.49 (quin, J = 7.1 Hz, 2H), 1.33 (s, 3H), 1.22 - 0.98 (m, 9H) ; LCMS (Method D): Rt = 1.65 min, m/z = 674.4 $[M+H]^+$; HPLC (Method A): Rt = 4.51 min, 99.80%.

Example 181. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(4-hydroxy-4-methylpiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 134)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2.5 equivalents of 4-methylpiperidin-4-ol and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C for 16 h. The reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(4-hydroxy-4-methylpiperidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 30.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.23 (m, 1H), 8.18 (d, J = 5.8 Hz, 1H), 7.80 - 7.65 (m, 1H), 7.34 - 7.19 (m, 2H), 7.11 - 6.96 (m, 1H), 6.66 (d, J = 5.8 Hz, 1H), 4.83 - 4.68 (m, 1H), 4.47 - 3.98 (m, 4H), 3.85 - 3.65 (m, 1H), 3.49 - 3.36 (m, 3H), 3.27 - 3.10 (m, 1H), 2.85 - 2.73 (m, 5H), 2.68 (d, J = 4.7 Hz, 3H), 2.48 - 2.44 (m, 4H), 2.43 - 2.20 (m, 5H), 1.71 - 1.59 (m, 2H), 1.51 - 1.39 (m, 4H), 1.24 - 0.95 (m, 12H); LCMS (Method G): Rt = 1.63 min, m/z = 702.7 $[M+H]^+$; HPLC (Method A): Rt = 5.18 min, 99.79%.

Example 182. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(6-oxo-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 141)

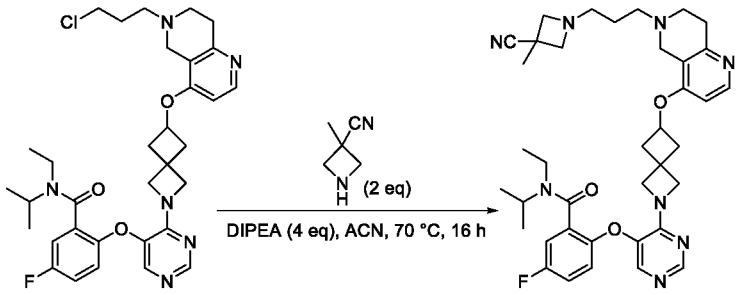


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of DIPEA and 2.5 equivalents of 2,5-diazaspiro[3.4]octan-6-one hydrochloride were used. The reaction was stirred at 70 °C for 16 h. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(6-oxo-2,5-

diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 94 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.19 - 8.14 (m, 1H), 8.08 (br s, 1H), 7.77 - 7.64 (m, 1H), 7.33 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.63 (m, 1H), 4.81 - 4.66 (m, 1H), 4.31 - 4.03 (m, 4H), 3.75-3.79 (m, 1H), 3.45 (br s, 2H), 3.09 - 2.90 (m, 2H), 2.93 -2.91 (m, 2H), 2.89 -2.78 (m, 4H), 2.67- 2.63 (m, 2H), 2.49 - 2.42 (m, 6H), 2.38 (t, J = 7.1 Hz, 2H), 2.35 - 2.10 (m, 4H), 1.51-1.47 (m, 2H), 1.26 - 0.94 (m, 9H); LCMS (Method B): Rt = 1.55 min, m/z = 713.2 $[M+H]^+$; HPLC (Method A): Rt = 4.76 min, 99.36%.

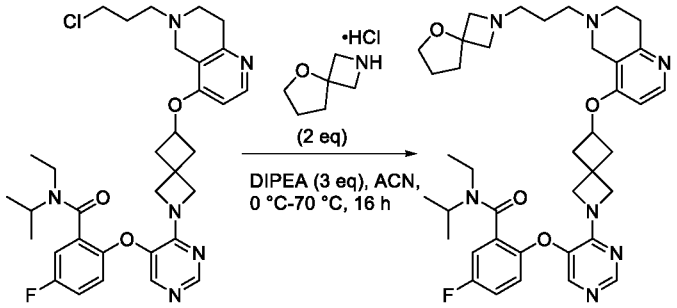
Example 183. 2-((4-(6-((6-(3-(3-Cyano-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 174)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 4 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(3-(3-cyano-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 45.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.36 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.63 (m, 1H), 4.79 - 4.68 (m, 1H), 4.47 - 4.05 (m, 4H), 3.80 - 3.71 (m, 1H), 3.45 - 3.41 (m, 2H), 3.40 (br s, 2H), 3.30 - 3.21 (m, 2H), 3.10 - 3.05 (m, 2H), 2.84 - 2.71 (m, 4H), 2.71 - 2.60 (m, 2H), 2.50 - 2.38 (m, 4H), 2.32 - 2.20 (m, 2H), 1.52 (s, 3H), 150 - 1.44 (m, 2H), 1.24 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.81 min, 683.4 $[M+H]^+$; HPLC (Method A): RT = 5.25 min, 98.12%.

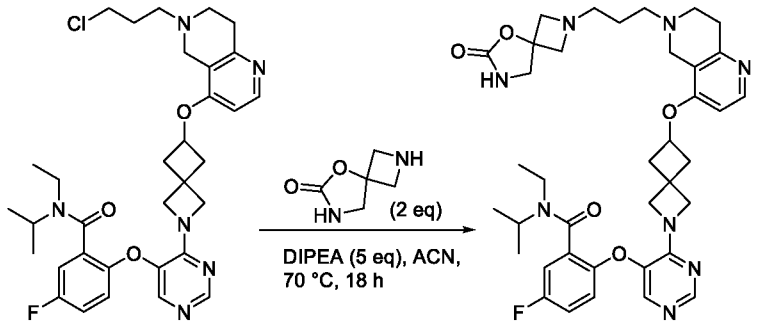
Example 184. 2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 295)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((4-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 35.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.20 - 8.15 (m, 1H), 7.78 - 7.64 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.80 - 4.70 (m, 1H), 4.33 - 4.03 (m, 4H), 3.76 (td, J = 6.6, 13.2 Hz, 1H), 3.65 (t, J = 6.8 Hz, 2H), 3.44 - 3.35 (m, 3H), 3.28 - 3.11 (m, 3H), 2.92 - 2.85 (m, 2H), 2.83 - 2.73 (m, 4H), 2.69 - 2.62 (m, 2H), 2.47 (br t, J = 7.4 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 2.32 - 2.21 (m, 2H), 2.03 - 1.95 (m, 2H), 1.80 (quin, J = 7.0 Hz, 2H), 1.50 (quin, J = 7.1 Hz, 2H), 1.28 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.77 min, m/z = 700.7 $[M+H]^+$; HPLC (Method A): Rt = 5.00 min, 99.60%.

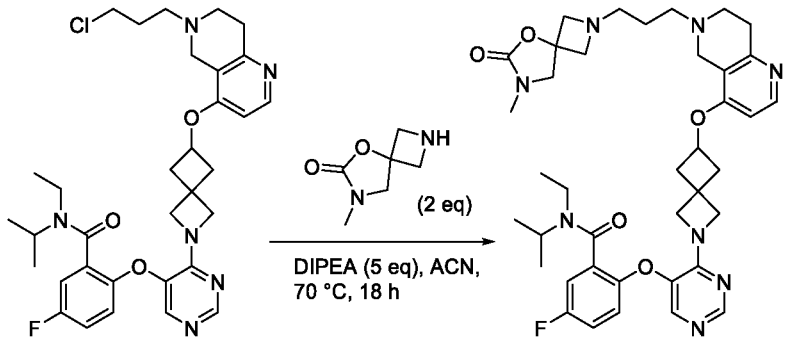
Example 185. *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 237)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 5-oxa-2,7-diazaspiro[3.4]octan-6-one was used, and the reaction was stirred in a pressure vial. The reaction was stirred at 70 °C. The crude product was purified by Prep HPLC (Method AJ) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 7.34%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.62 (s, 1H), 7.33 - 7.21 (m, 2H), 7.09 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.46 - 4.07 (m, 4H), 3.80 - 3.70 (m, 1H), 3.64 (s, 2H), 3.44 - 3.36 (m, 5H), 3.27 - 3.17 (m, 3H), 2.83 - 2.74 (m, 4H), 2.68 - 2.63 (m, 2H), 2.48 - 2.41 (m, 2H), 2.30 - 2.22 (m, 2H), 1.51 (quin, J = 7.1 Hz, 2H), 1.23 - 0.98 (m, 9H), two protons merged with solvent peaks; LCMS (Method B): Rt = 1.03 min, m/z = 715.4 $[M+H]^+$; HPLC (Method A): Rt = 4.59 min, 98.94%.

Example 186. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(7-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 242)

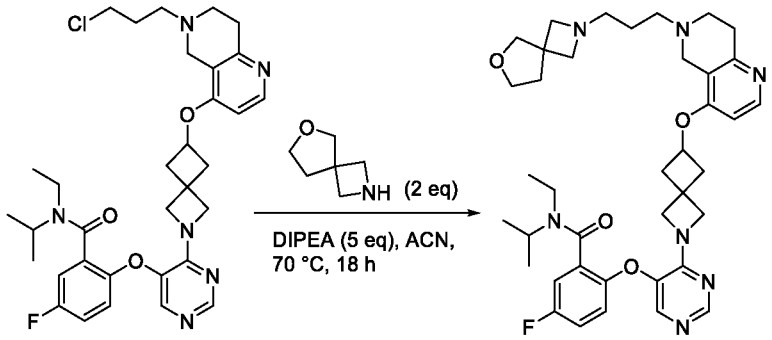


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 7-methyl-5-oxa-2,7-diazaspiro[3.4]octan-6-one was used, and the reaction was stirred in a pressure vial. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-(((6-(3-(7-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 14.69%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 6.99 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.80 - 4.69 (m, 1H), 4.45 - 4.07 (m, 4H), 3.81 - 3.73 (m, 1H), 3.70 (s, 2H), 3.47 - 3.36 (m, 5H), 3.27 - 3.19 (m, 3H), 2.83 - 2.77 (m, 4H), 2.73 (s, 3H), 2.70 - 2.64 (m, 2H), 2.48 - 2.40 (m, 4H), 2.30 - 2.21 (m, 2H), 1.51 (quin, J = 7.0 Hz, 2H), 1.23 - 0.98 (m, 9H); LCMS (Method G): Rt = 1.63 min, m/z = 729.7 $[M+H]^+$; HPLC (Method A): Rt = 4.74 min, 98.25%.

Example 187. 2-((4-(6-(((6-(3-(6-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 270)

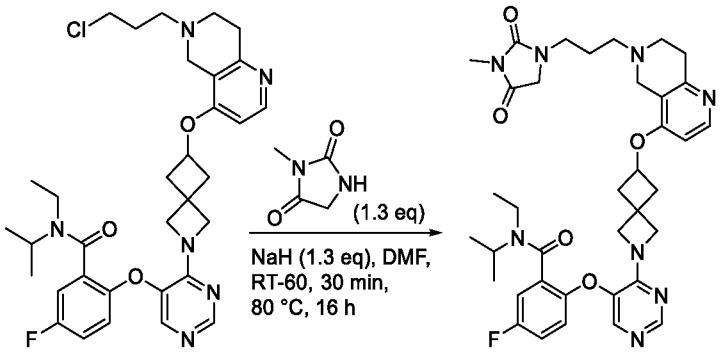


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-(((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 6-oxa-2-azaspiro[3.4]octane was used, and the reaction was stirred in a pressure vial. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-(((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 44.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 - 7.63 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 - 7.01 (m, 1H), 6.70 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.47 - 4.08 (m, 4H), 3.81 - 3.71 (m, 1H), 3.67 (s, 2H), 3.63 (t, J = 6.9 Hz, 2H), 3.39 (s, 2H), 3.28 - 3.13 (m, 1H), 3.09 - 3.02 (m, 4H), 2.81 - 2.74 (m, 4H), 2.67 - 2.63 (m, 2H), 2.72 - 2.59 (m, 2H), 2.48 - 2.43 (m, 1H), 2.37 (br t, J = 7.1 Hz, 2H), 2.30 - 2.22 (m, 2H), 1.97 (t, J = 6.9 Hz, 2H), 1.49 (quin, J = 7.1 Hz, 2H), 1.22 - 0.98 (m, 9H); LCMS (Method G): Rt = 1.68 min, m/z = 700.7 $[M+H]^+$; HPLC (Method A): Rt = 4.79 min, 97.71%.

Example 188. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methyl-2,4-dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 292)

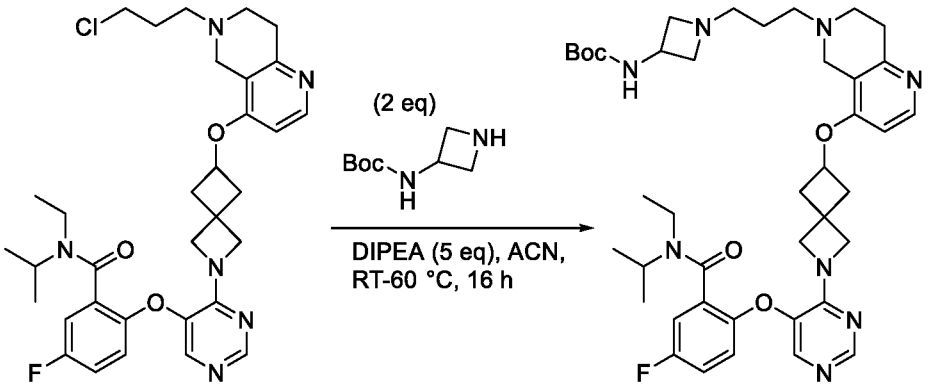


This reaction was performed following the same procedure in two batches, 100 mg and 200 mg batches.

In a 25 mL round bottom flask under a nitrogen atmosphere, 3-methylimidazolidine-2,4-dione (47.6 mg, 0.417 mmol) was added in DMF (1 mL). To this solution, sodium hydride (16.69 mg, 0.417 mmol) was added at RT. The reaction was stirred at 60 °C for 30 min. The reaction was cooled to RT and 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (200 mg, 0.321 mmol) was added. The reaction was stirred at 80 °C for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was cooled to RT and quenched with water (6 mL). The reaction was concentrated under reduced pressure to obtain the crude product. Both batches were mixed and purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methyl-2,4-dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (48

mg, 14.24% combined yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.78 - 7.66 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.82 - 4.69 (m, 1H), 4.45 - 4.08 (m, 4H), 3.97 (s, 2H), 3.83 - 3.69 (m, 1H), 3.42 (s, 2H), 3.40 - 3.34 (m, 3H), 3.27 - 3.15 (m, 1H), 2.83 - 2.75 (m, 7H), 2.73 - 2.65 (m, 2H), 2.30 - 2.21 (m, 2H), 1.74 (quin, J = 6.8 Hz, 2H), 1.23 - 0.97 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.67 min, m/z = 701.6 $[M+H]^+$; HPLC (Method A): Rt = 4.89 min, 98.46%.

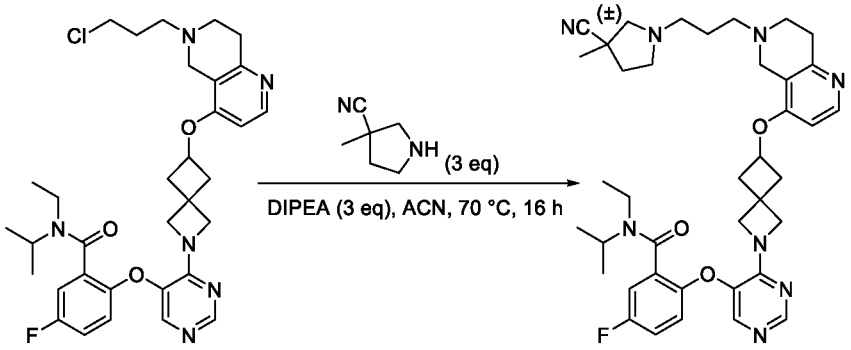
Example 189. *tert*-Butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate (Compound No. 153)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of *tert*-butyl azetidin-3-ylcarbamate was used. The reaction was stirred in a pressure vial. The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *tert*-butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate (440 mg, 84% yield) as a solid. LCMS (Method G): Rt = 1.82 min, m/z = 759.7 $[M+H]^+$; 81.13%. This compound (60 mg) was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *tert*-Butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate as a solid (22.5 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H),

8.17 (d, J = 5.7 Hz, 1H), 7.77 - 7.64 (m, 1H), 7.34 - 7.21 (m, 3H), 7.11 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.45 - 4.08 (m, 4H), 4.04 - 3.95 (m, 1H), 3.82 - 3.69 (m, 1H), 3.45 (br t, J = 7.0 Hz, 2H), 3.39 (s, 2H), 3.29 - 3.12 (m, 2H), 2.83 - 2.75 (m, 4H), 2.73 - 2.63 (m, 4H), 2.47 - 2.42 (m, 2H), 2.38 - 2.32 (m, 2H), 2.30 - 2.22 (m, 2H), 1.53 - 1.43 (m, 2H), 1.37 (s, 9H), 1.24 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.80 min, m/z = 759.8 $[M+H]^+$; HPLC (Method A): Rt = 5.93 min, 99.60%.

Example 190. (±)-2-((4-(6-((6-(3-(3-Cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 181)

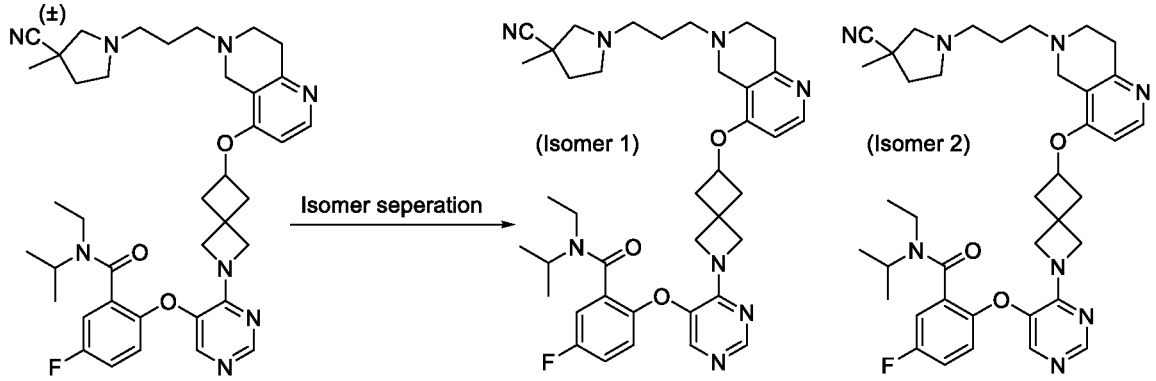


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of DIPEA and 3 equivalents of (±)-3-methylpyrrolidine-3-carbonitrile were used. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((4-(6-((6-(3-(3-cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 13.28%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 - 8.25 (m, 1H), 8.23 - 8.14 (m, 1H), 7.78 - 7.64 (m, 1H), 7.37 - 7.19 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.79 - 4.68 (m, 1H), 4.49 - 4.02 (m, 4H), 3.82 - 3.69 (m, 1H), 3.48 - 3.34 (m, 4H), 3.28 - 3.08 (m, 1H), 2.97 (d, J = 9.3 Hz, 1H), 2.85 - 2.71 (m, 5H,), 2.72 - 2.63 (m, 2H), 2.53 - 2.40 (m, 4H), 2.37 (d, J = 9.4 Hz, 1H), 2.32 - 2.17 (m, 3H), 1.90 - 1.76 (m, 1H), 1.73 - 1.57 (m, 2H), 1.40 (s, 3H), 1.22 - 0.95 (m, 9H); LCMS (Method G): Rt = 1.89 min, m/z = 697.3 $[M+H]^+$; HPLC (Method A): Rt = 5.97 min, 98.71%. Chiral SFC (Method AS): Peak 1: Rt = 9.19 min, 45.84%; Peak 2: Rt = 10.27 min, 53.88 %.

Example 191. (*E1*)-2-((4-(6-((6-(3-(3-Cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 198)

Example 192. (*E2*)-2-((4-(6-((6-(3-(3-Cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 199)



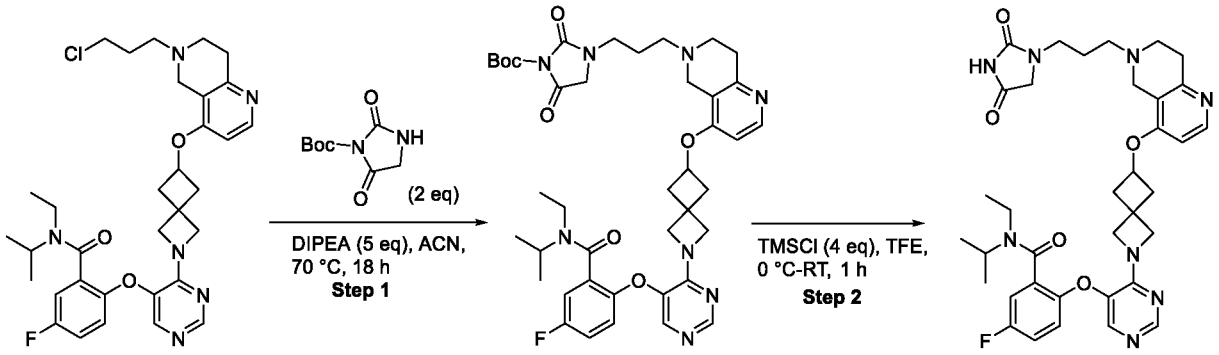
(±)-2-((4-(6-((6-(3-(3-Cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (60 mg) was purified by chiral Prep SFC (Method I) to obtain both isomers,(*E1*)-2-((4-(6-((6-(3-(3-cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (25 mg, 41.4% yield) and (*E2*)-2-((4-(6-((6-(3-(3-cyano-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (15 mg, 24.39%) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.21 - 8.15 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.82 - 4.65 (m, 1H), 4.51 - 4.03 (m, 4H), 3.82 - 3.68 (m, 1H), 3.46 - 3.35 (m, 4H), 3.30 - 3.08 (m, 1H), 2.97 (d, J = 9.4 Hz, 1H), 2.84 - 2.73 (m, 5H), 2.71 - 2.62 (m, 2H), 2.49 - 2.42 (m, 4H), 2.37 (d, J = 9.4 Hz, 1H), 2.31 - 2.16 (m, 3H), 1.91 - 1.74 (m, 1H), 1.72 - 1.60 (m, 2H), 1.40 (s, 3H), 1.28 - 0.93 (m, 9H); LCMS (Method D): Rt = 1.89 min, m/z = 697.4 $[M+H]^+$; HPLC (Method A): Rt = 5.32 min, 99.42%; Chiral SFC (Method Y): Rt = 23. 82 min, 99.36%.

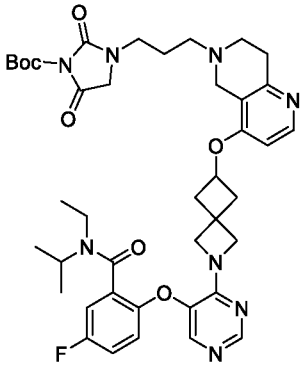
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.21 - 8.16 (m, 1H), 7.76 - 7.66 (m, 1H), 7.37 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.80 - 4.69 (m, 1H), 4.37 - 4.06 (m, 4H), 3.75 (p, J = 6.6 Hz, 1H), 3.51 - 3.35 (m, 4H), 3.28 - 3.10 (m, 1H), 2.97 (d, J = 9.4 Hz, 1H), 2.85 - 2.72 (m, 5H), 2.70 - 2.64 (m, 2H), 2.49 - 2.41 (m, 4H), 2.37

(d, J = 9.4 Hz, 1H), 2.32 - 2.18 (m, 3H), 1.86 - 1.75 (m, 1H), 1.67 (p, J = 7.3 Hz, 2H), 1.40 (s, 3H), 1.26 - 0.95 (m, 9H); LCMS (Method D): Rt = 1.89 min, m/z = 697.4 $[M+H]^+$, HPLC (Method A) Rt = 5.32 min, 97.57%; Chiral SFC (Method Y): Rt = 27.42 min, 98.79%.

Example 193. 2-((4-(6-(((6-(3-(2,4-Dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 245)



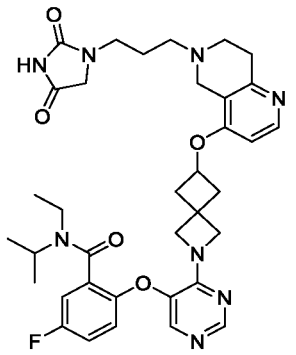
Step 1. tert-Butyl 3-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)-2,5-dioxoimidazolidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-(((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of *tert*-butyl 2,5-dioxoimidazolidine-1-carboxylate was used. The reaction was stirred at 70 °C. The reaction was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 9-10% MeOH in DCM) to obtain *tert*-butyl 3-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)-2,5-

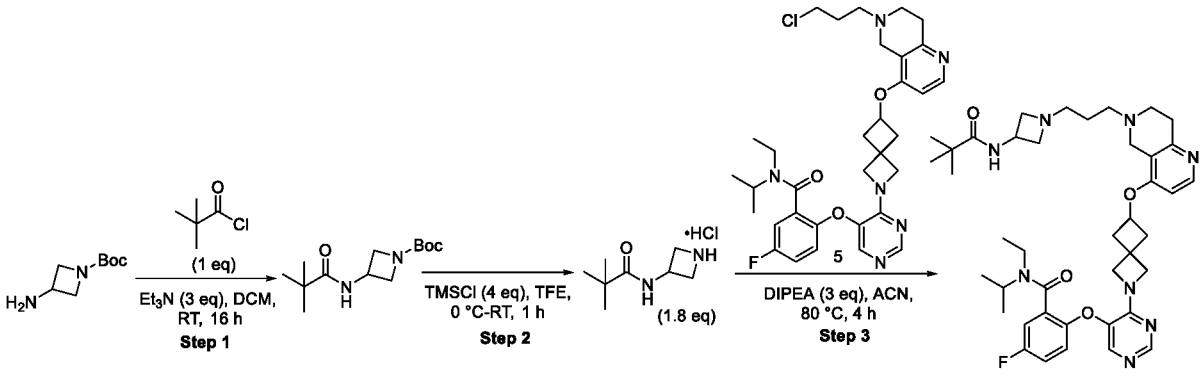
dioxoimidazolidine-1-carboxylate (80 mg, 20.82% yield) as a liquid. LCMS (Method G): Rt = 1.95 min, m/z = 787.2 $[M+H]^+$; 98.58%.

Step 2. 2-((4-(6-((6-(3-(2,4-Dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

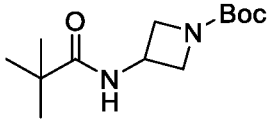


In a 25 mL round bottom flask, *tert*-butyl 3-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)-2,5-dioxoimidazolidine-1-carboxylate (80 mg, 0.102 mmol) was added in 2,2,2-trifluoroethanol (10 mL) . To this solution, TMSCl (0.052 mL, 0.407 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to obtain 2-((4-(6-((6-(3-(2,4-dioxoimidazolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (22.54 mg, 31.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.99 (s, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.65 (m, 1H), 4.82 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.85 (s, 2H), 3.81 - 3.70 (m, 1H), 3.44 - 3.37 (m, 5H), 3.28 - 3.12 (m, 2H), 4.83 - 2.74 (m, 4H), 2.69 - 2.64 (m, 2H), 2.31 - 2.20 (m, 2H), 1.74 (quin, *J* = 7.1 Hz, 2H), 1.24 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.73 min, m/z = 687.4 $[M+H]^+$; HPLC (Method A): Rt = 4.79 min, 98.43%.

Example 194. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-pivalamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 206)

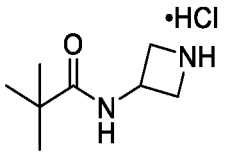


Step 1. tert-Butyl 3-pivalamidoazetidine-1-carboxylate



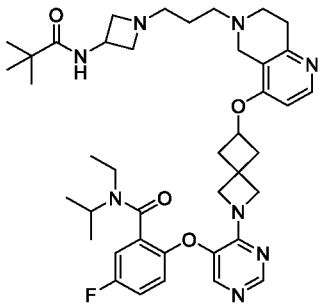
In a 100 mL two neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-aminoazetidine-1-carboxylate (0.455 mL, 2.90 mmol) was added in DCM. To this solution, Et_3N (1.214 mL, 8.71 mmol) and trimethylacetyl chloride (0.358 mL, 2.90 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH DCM). After completion, the reaction was quenched with aq. $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford *tert*-butyl 3-pivalamidoazetidine-1-carboxylate (0.737g, 99% yield) as a solid. ^1H NMR (400 MHz, $CDCl_3$): δ 6.05 - 5.89 (m, 1H), 4.66 - 4.56 (m, 1H), 4.28 (dd, J = 8.0, 9.5 Hz, 2H), 3.71 (dd, J = 5.3, 9.8 Hz, 2H), 1.46 (s, 9H), 1.23 (s, 9H); LCMS (Method B): Rt = 1.80 min, m/z = 257.2 $[M+H]^+$, 99.53%. This material was used without further purification.

Step 2. N-(Azetidin-3-yl)pivalamide hydrochloride



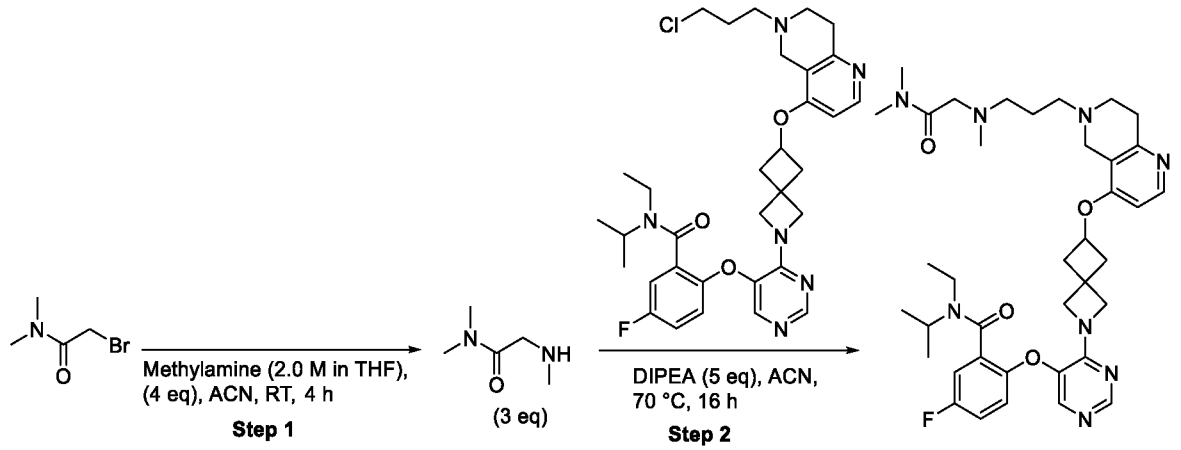
In a 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-pivalamidoazetidine-1-carboxylate (100 mg, 0.390 mmol) was added in TFE (2 mL). TMSCl (0.199 mL, 1.560 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure and triturated with MTBE (2 x 10 mL) to afford *N*-(azetidin-3-yl)pivalamide hydrochloride (90 mg, 68.4% yield) as a viscous liquid. This material was used without further purification.

Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-pivalamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

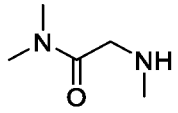


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1.8 equivalents of *N*-(azetidin-3-yl)pivalamide hydrochloride and 3 equivalents of DIPEA were used. The reaction was stirred at 80 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-pivalamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (24.72 mg, 10.10% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.20 - 8.15 (m, 1H), 7.78 - 7.64 (m, 2H), 7.35 - 7.20 (m, 2H), 7.12 - 6.99 (m, 1H), 6.70 - 6.63 (m, 1H), 4.82 - 4.70 (m, 1H), 4.35 - 4.04 (m, 5H), 3.81 - 3.71 (m, 1H), 3.57 - 3.44 (m, 2H), 3.40 (s, 2H), 3.29 - 3.11 (m, 2H), 2.96 - 2.73 (m, 6H), 2.73 - 2.63 (m, 3H), 2.49 - 2.37 (m, 3H), 2.32 - 2.20 (m, 2H), 1.58 - 1.44 (m, 2H), 1.27 - 0.97 (m, 18H); LCMS (Method G): Rt = 1.70 min, m/z = 743.7 $[M+H]^+$; HPLC (Method E): Rt = 3.18 min, 97.45%.

Example 195. 2-((4-(6-((6-(3-((2-(Dimethylamino)-2-oxoethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 248)

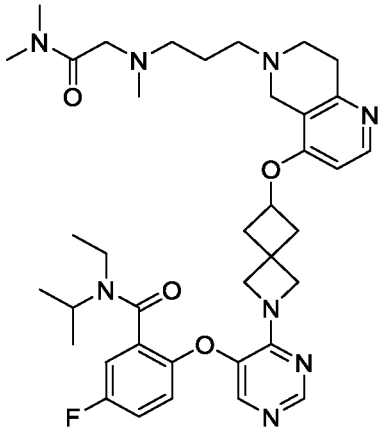


Step 1. N,N-Dimethyl-2-(methylamino)acetamide



To a stirred solution of methylamine (12.05 mL, 24.09 mmol, 2M in THF) in acetonitrile (10 mL), 2-bromo-*N*,*N*-dimethylacetamide (0.717 mL, 6.02 mmol) was added at 0 °C. The temperature was maintained below 10 °C for 10 min, then the reaction was warmed to RT and stirred for 4 h. The reaction was monitored by TLC (50% EtOAc in hexane). The reaction was concentrated under reduced pressure. The crude material was quenched with 2 M NaOH (2mL) and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to obtain *N*,*N*-dimethyl-2-(methylamino)acetamide (0.29 g, 48.3% yield) as a liquid. LCMS-ELSD (Method B): Rt = 0.28 min, m/z = 117.3 $[M+H]^+$; 99.92%.

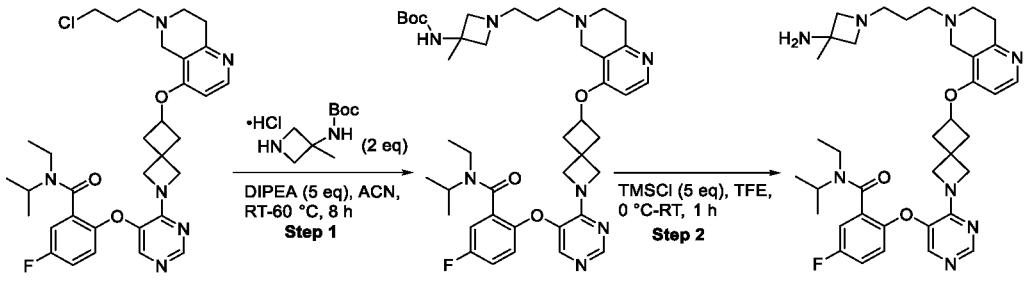
Step 2. 2-((4-(6-((6-(3-((2-(Dimethylamino)-2-oxoethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



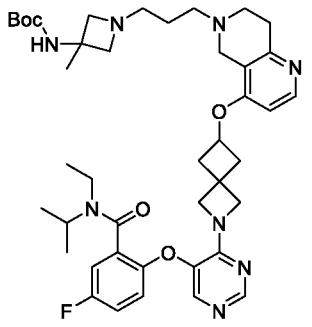
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of *N*,*N*-dimethyl-2-(methylamino)acetamide was used. The reaction was stirred at 70 °C. The reaction was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(3-((2-(dimethylamino)-2-oxoethyl)(methyl)amino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 6.02%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.76 - 7.64 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.66 (br d, J = 5.8 Hz, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.08 (m, 5H), 3.79 - 3.71 (m, 1H), 3.40 (br s, 5H), 3.13 - 3.00 (m, 6H), 2.78 (s, 7H), 2.40 (br t, J = 6.9 Hz, 2H), 2.29 - 2.22 (m, 2H), 2.18 (s, 3H), 1.68 - 1.60 (m, 2H), 1.22 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.80 min, m/z = 703.7 $[M+H]^+$; HPLC (Method A): Rt = 4.87 min, 97.73%.

Example 196. 2-((4-(6-((6-(3-(3-Amino-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 196)

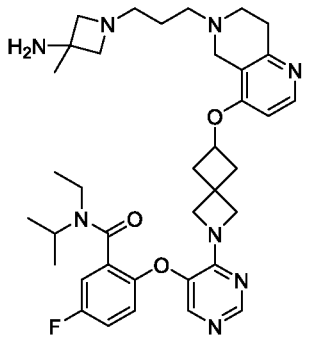


Step 1. tert-Butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)-3-methylazetidin-3-yl)carbamate



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of *tert*-butyl (3-methylazetidin-3-yl)carbamate hydrochloride was used. The reaction was stirred in a pressure vial. After completion, water was added and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 20% MeOH in DCM) to obtain *tert*-butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)-3-methylazetidin-3-yl)carbamate (0.23 g, 20.80% yield) as a solid. LCMS (Method G): Rt = 1.97 min, m/z = 773.8 $[M+H]^+$; 67.36%.

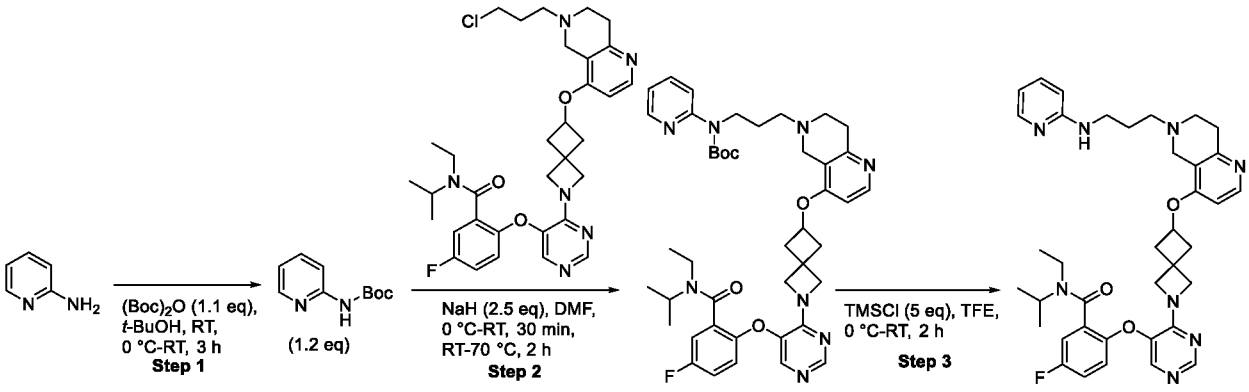
Step 2. 2-((4-(6-((6-(3-(3-Amino-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



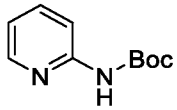
To a stirred solution of *tert*-butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)-3-methylazetidin-3-yl)carbamate (230 mg, 0.298 mmol) in TFE (3 mL), TMSCl (0.190 mL, 1.488 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After

completion, the reaction was concentrated under reduced pressure to obtain crude 2-((4-(6-((6-(3-(3-amino-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH), then by Prep HPLC (Method B) to obtain 2-((4-(6-((6-(3-(3-amino-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (2.96 mg, 1.48 yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.68 - 6.64 (m, 1H), 4.78 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.81 - 3.66 (m, 1H), 3.42 - 3.38 (m, 4H), 3.27 - 3.21 (m, 1H), 3.11 (br d, J = 7.0 Hz, 2H), 2.78 (br d, J = 5.3 Hz, 4H), 2.65 (br d, J = 5.3 Hz, 2H), 2.38 (br t, J = 7.2 Hz, 2H), 2.30 - 2.22 (m, 2H), 1.48 (quin, J = 7.3 Hz, 2H), 1.26 (s, 3H), 1.22 - 0.98 (m, 9H), five protons merged with solvent peaks; LCMS (Method A): Rt = 2.09 min, m/z = 673.4 $[M+H]^+$; HPLC (Method A): Rt = 4.48 min, 97.26%.

Example 197. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyridin-2-ylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 169)



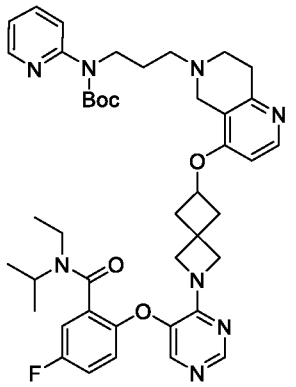
Step 1. tert-Butyl pyridin-2-ylcarbamate



To a stirred solution of $(Boc)_2O$ (2.69 mL, 11.69 mmol) in *t*-BuOH (20 mL), pyridin-2-amine (1 g, 10.63 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred at RT for 3 h. The reaction progress was monitored by TLC (100% EtOAc). The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash

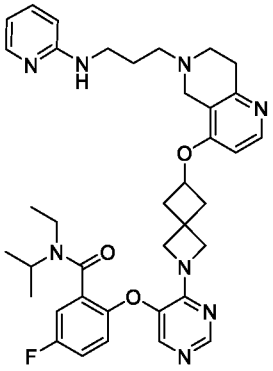
column chromatography using EtOAc in hexane (product eluted at 50% EtOAc in hexane) to obtain *tert*-butyl pyridin-2-ylcarbamate (1.2 g, 57.6% yield) as a solid. LCMS (Method F): Rt = 1.82 min, m/z = 195.1 $[M+H]^+$; 99.10%.

Step 2. tert-Butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)(pyridin-2-yl)carbamate



To a stirred solution of *tert*-butyl pyridin-2-ylcarbamate (0.112 g, 0.578 mmol) in DMF (2 mL), NaH (0.048 g, 1.204 mmol) was added at 0 °C. The reaction was stirred at RT for 30 min. To this reaction mixture, 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.3 g, 0.481 mmol) was added at RT, and the reaction was stirred at 70 °C for 2 h. The reaction progress was monitored by TLC (7% MeOH in DCM). The reaction was quenched with ammonium chloride solution (10 mL) and extracted with 10% MeOH in DCM (2 x 20 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to obtain *tert*-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)(pyridin-2-yl)carbamate (0.130 g, 22.48% yield) as an oil. LCMS (Method D): Rt = 2.19 min, m/z = 781.5 $[M+H]^+$; 65.03%.

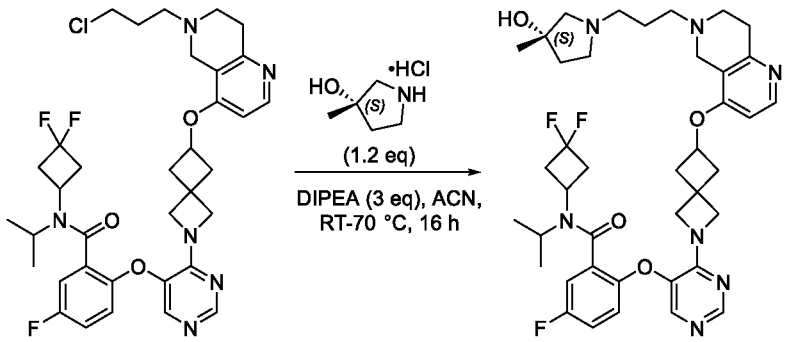
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(pyridin-2-ylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *tert*-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)(pyridin-2-yl)carbamate (0.110 g, 0.141 mmol) in 2,2,2-trifluoroethanol (1 mL) under a nitrogen atmosphere, TMSCl (0.089 mL, 0.704 mmol) was added at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc (2 x 10 mL). The EtOAc layer was decanted, and the solid was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The obtained product was impure. Therefore, the product was re-purified by Prep HPLC (Method F) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(pyridin-2-ylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (7.42 mg, 7.68% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.94 (dd, J = 1.9, 5.6 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.36 - 7.21 (m, 3H), 7.10 - 7.00 (m, 1H), 6.70 - 6.65 (m, 1H), 6.54 - 6.41 (m, 2H), 6.48 (t, J = 5.4 Hz, 1H), 4.79 - 4.70 (m, 1H), 4.45 - 4.06 (m, 4H), 3.81 - 3.68 (m, 1H), 3.46 (br s, 2H), 3.44 - 3.37 (m, 1H), 3.30 - 3.10 (m, 3H), 2.87 - 2.69 (m, 6H), 2.63 - 2.54 (m, 2H), 2.31 - 2.21 (m, 2H), 1.77 (quin, J = 6.8 Hz, 2H), 1.22 - 0.95 (m, 9H); LCMS (Method D): Rt = 1.86 min, m/z = 681.4 $[M+H]^+$; HPLC (Method A): Rt = 5.38 min, 99.03%.

Example 198. (*S*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

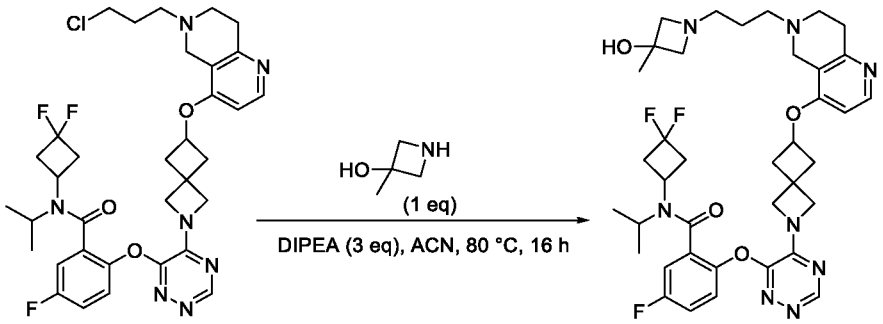
azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 244)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, staring with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 1.2 equivalents (*S*)-3-methylpyrrolidin-3-ol hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The crude was purified by Prep HPLC (Method B) to afford (*S*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

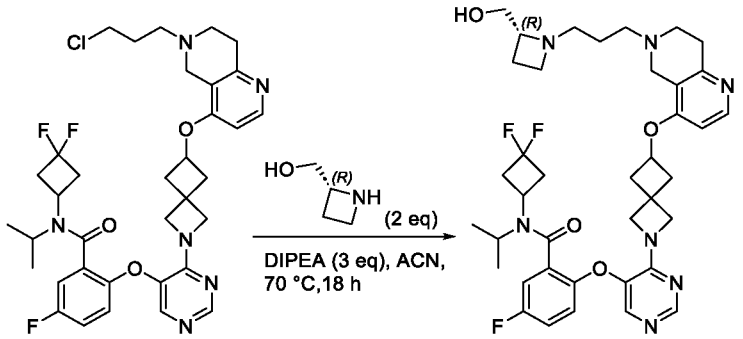
Yield: 22.14%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, *J* = 2.8, 8.1 Hz, 1H), 7.27 (dt, *J* = 2.9, 8.5 Hz, 1H), 7.06 (br dd, *J* = 4.3, 9.0 Hz, 1H), 6.66 (d, *J* = 5.8 Hz, 1H), 4.74 (quin, *J* = 6.6 Hz, 1H), 4.47 (s, 1H), 4.35 - 4.05 (m, 4H), 3.99 - 3.85 (m, 1H), 3.82 - 3.46 (m, 3H), 3.40 (s, 2H), 2.85 - 2.62 (m, 9H), 2.61 - 2.55 (m, 1H), 2.41 (s, 2H), 2.40 - 2.32 (m, 3H), 2.31 - 2.21 (m, 2H), 1.80 - 1.55 (m, 4H), 1.50 - 1.28 (m, 1H), 1.23 (s, 3H), 1.10 (br d, *J* = 5.9 Hz, 3H), 1.02 (br d, *J* = 5.9 Hz, 3H); LCMS (Method G): Rt = 1.87 min, m/z = 750.4 $[M+H]^+$; HPLC (Method A): Rt = 5.19 min, 98.13%; Chiral SFC (Method K): Rt = 5.47 min, 98.86%.

Example 199. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((5-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (Compound No. 205)



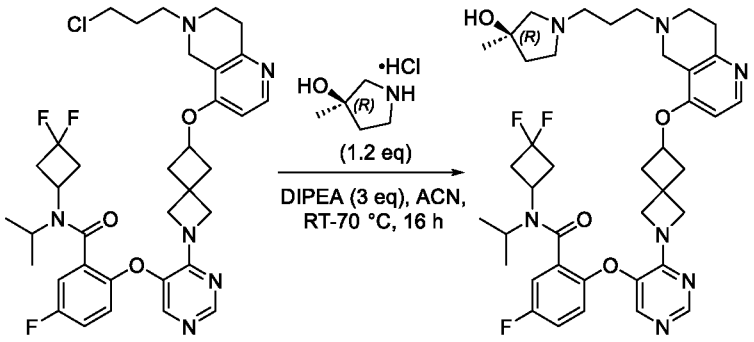
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 1 equivalent of 3-methylazetidin-3-ol, except that 3 equivalents of DIPEA was used. The reaction was stirred at 80 °C for 16 h. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((5-(6-((6-(3-(3-hydroxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide as a solid. Yield: 22.33%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.21-8.18 (m, 1H), 7.49 - 7.44 (m, 1H), 7.43 - 7.36 (m, 2H), 6.71 - 6.64 (m, 1H), 5.10 - 5.07 (m, 1H), 4.84 - 4.75 (m, 1H), 4.69 - 4.49 (m, 2H), 4.31 - 4.12 (m, 2H), 3.93 - 3.78 (m, 2H), 3.71 - 3.57 (m, 2H), 3.44 - 3.38 (m, 4H), 3.21 - 3.14 (m, 3H), 2.87 - 2.74 (m, 6H), 2.69 - 2.66 (m, 3H), 2.48 - 2.39 (m, 4H), 1.55 - 1.46 (m, 2H), 1.33 (s, 3H), 1.08 (br s, 3H), 0.71 (br s, 3H); LCMS (Method B): Rt = 1.19 min, m/z = 737.5 $[M+H]^+$; HPLC (Method A): Rt = 4.98 min, 97.97%.

Example 200. (*R*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(2-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 239)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of (*R*)-azetidin-2-ylmethanol, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The reaction was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the product (150 mg). The obtained product was impure. Therefore, it was re-purified by Prep HPLC (Method C) to afford (R)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(2-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 31.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.78 (s, 1H), 7.36 (dd, *J* = 2.9, 8.2 Hz, 1H), 7.27 (dt, *J* = 3.0, 8.6 Hz, 1H), 7.06 (dd, *J* = 4.3, 9.0 Hz, 1H), 6.65 (d, *J* = 5.7 Hz, 1H), 4.74 (quin, *J* = 6.7 Hz, 1H), 4.44 - 4.06 (m, 5H), 3.98 - 3.86 (m, 1H), 3.79 - 3.48 (m, 3H), 3.39 (s, 2H), 3.26 - 3.20 (m, 1H), 3.06 - 2.97 (m, 1H), 2.83 - 2.63 (m, 10H), 2.62 - 2.54 (m, 1H), 2.48 - 2.44 (m, 2H), 2.32 - 2.23 (m, 3H), 1.94 - 1.85 (m, 1H), 1.75 (quin, *J* = 9.1 Hz, 1H), 1.51 (quin, *J* = 7.1 Hz, 2H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.02 (d, *J* = 6.1 Hz, 3H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.81 min, m/z = 736.6 $[M+H]^+$; HPLC (Method A): Rt = 5.14 min, 98.62%; Chiral SFC (Method AD): Rt = 3.48 min, 100%.

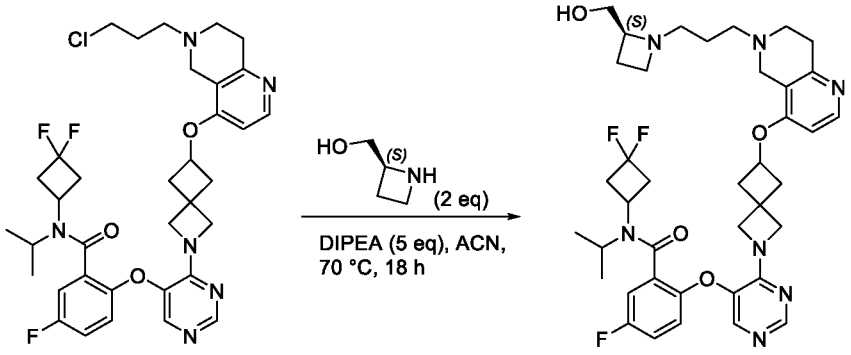
Example 201. (*R*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 252)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 1.2 equivalents of (*R*)-3-methylpyrrolidin-3-ol hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (R)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-hydroxy-3-methylpyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 19.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, J = 3.0, 8.5 Hz, 1H), 7.27 (dt, J = 3.3, 8.6 Hz, 1H), 7.06 (dd, J = 4.0, 9.0 Hz, 1H), 6.66 (d, J = 5.5 Hz, 1H), 4.74 (quin, J = 6.5 Hz, 1H), 4.47 (s, 1H), 4.29 - 4.05 (m, 4H), 3.99 - 3.83 (m, 1H), 3.79 - 3.45 (m, 2H), 3.40 (s, 2H), 3.39 - 3.35 (m, 1H), 3.30 - 3.14 (m, 1H), 2.85 - 2.66 (m, 7H), 2.59 - 2.54 (m, 2H), 2.48 - 2.46 (m, 1H), 2.41 (s, 2H), 2.38 (br t, J = 7.5 Hz, 2H), 2.35 - 2.32 (m, 1H), 2.31 - 2.23 (m, 2H), 1.79 - 1.59 (m, 4H), 1.23 (s, 3H), 1.10 (br d, J = 6.0 Hz, 3H), 1.02 (br d, J = 6.0 Hz, 3H); LCMS (Method G): Rt = 1.98 min, m/z = 750.7 $[M+H]^+$; HPLC (Method A): Rt = 5.21 min, 98.97%; Chiral SFC (Method U): Rt = 3.42 min, 97.65%

Example 202. (*S*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(2-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 279)

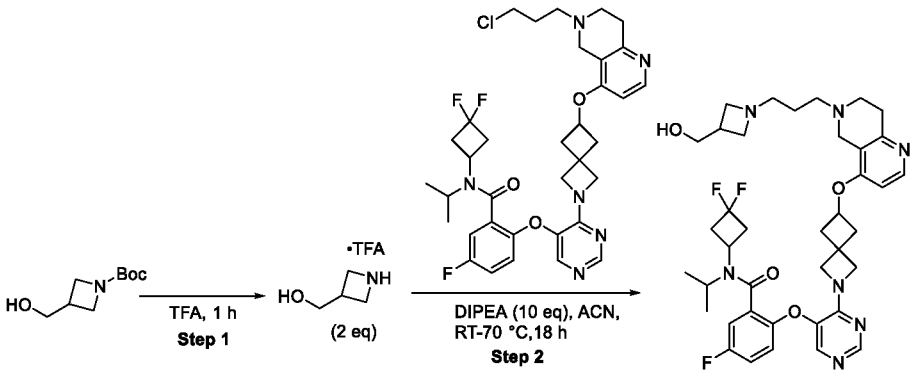


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-

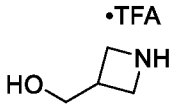
(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of (*S*)-azetidin-2-ylmethanol. The reaction was stirred at 70 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AK). The fractions were concentrated under reduced pressure, and the solid was neutralized with a saturated sodium bicarbonate solution. The aqueous layer was extracted with DCM, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and lyophilized to obtain (*S*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(2-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 17.37%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.17 (d, *J* = 5.6 Hz, 1H), 7.78 (s, 1H), 7.36 (dd, *J* = 2.9, 8.2 Hz, 1H), 7.27 (dt, *J* = 2.9, 8.6 Hz, 1H), 7.06 (dd, *J* = 4.3, 9.1 Hz, 1H), 6.65 (d, *J* = 5.8 Hz, 1H), 4.74 (quin, *J* = 6.7 Hz, 1H), 4.44 - 4.06 (m, 5H), 3.97 - 3.86 (m, 1H), 3.78 - 3.49 (m, 3H), 3.39 (s, 2H), 3.26 - 3.20 (m, 1H), 3.05 - 2.97 (m, 1H), 2.83 - 2.63 (m, 10H), 2.62 - 2.55 (m, 1H), 2.47 - 2.43 (m, 2H), 2.31 - 2.23 (m, 3H), 1.94 - 1.85 (m, 1H), 1.74 (quin, *J* = 9.0 Hz, 1H), 1.50 (quin, *J* = 7.2 Hz, 2H), 1.10 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 5.8 Hz, 3H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.85 min, m/z = 736.4 $[M+H]^+$; HPLC (Method A): Rt = 5.20 min, 99.50%; Chiral SFC (Method AE): Rt = 1.68 min, 97.86%.

Example 203. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 240)



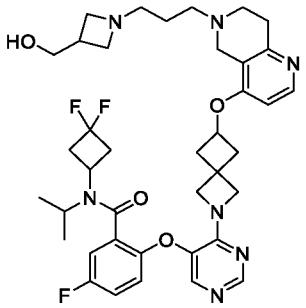
Step 1. Azetidin-3-ylmethanol 2,2,2-trifluoroacetic acid



In a 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (1 g, 5.34 mmol) was added in TFA (15 mL). The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain the crude azetidin-3-ylmethanol 2,2,2-trifluoroacetic acid (2 g). This material was used without further purification.

Note: Crude product contained excess TFA.

Step 2. N-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



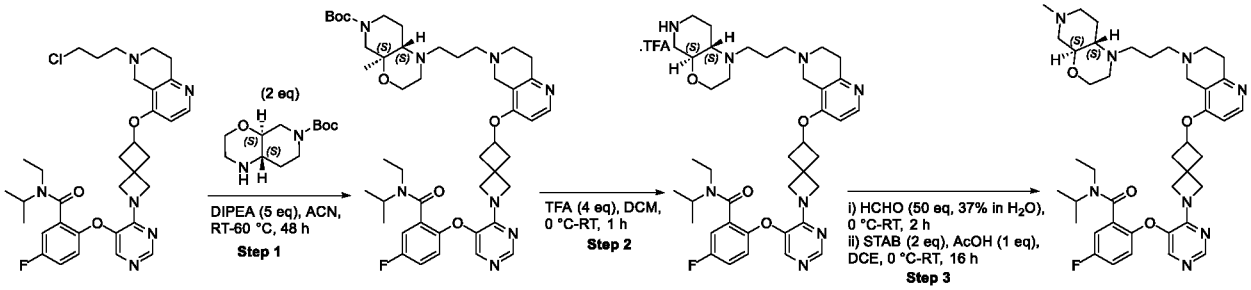
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of azetidin-3-ylmethanol 2,2,2-trifluoroacetic acid, except that 10 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The reaction was concentrated under reduced pressure, water was added, and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((6-(3-(3-(hydroxymethyl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 4.55%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.78 (s, 1H), 7.36 (dd, J = 3.0, 8.2 Hz, 1H), 7.27 (dt, J = 2.9, 8.6 Hz, 1H), 7.06 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.7 Hz, 1H), 4.74 (quin, J = 6.8 Hz, 1H), 4.53 (t, J = 5.3 Hz, 1H), 4.30 - 4.07 (m, 4H), 3.96 - 3.66 (m, 2H), 3.49 - 3.45 (m, 2H), 3.38 (s, 2H), 3.14 (t, J = 7.2 Hz, 2H), 2.83 - 2.69 (m, 8H), 2.67 - 2.63 (m, 2H), 2.47 - 2.38 (m, 4H), 2.36 - 2.32 (m, 3H), 2.26 (dd, J

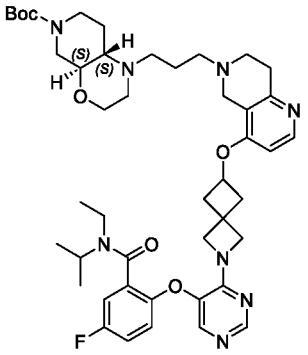
= 6.6, 12.8 Hz, 2H), 1.46 (quin, *J* = 7.1 Hz, 2H), 1.15 - 0.94 (m, 6H); LCMS (Method G): Rt = 1.81 min, m/z = 735.6 $[M+H]^+$; HPLC (Method A): Rt = 5.04 min, 97.70%.

Example 204. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-6-methyloctahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 136)

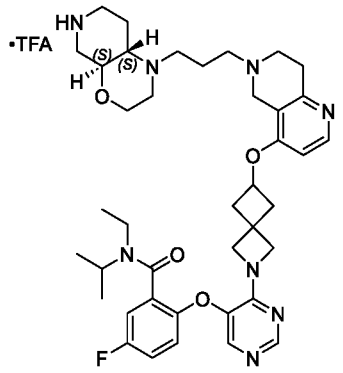


Step 1. tert-Butyl (4aS,8aS)-1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate



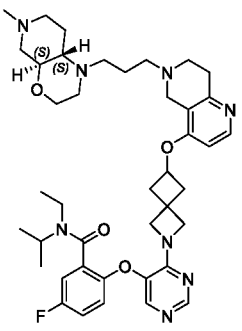
To a solution of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.3 g, 0.481 mmol) in ACN (5 mL), DIPEA (0.419 mL, 2.407 mmol) and *tert*-butyl (4a*S*,8a*S*)-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (0.233 g, 0.963 mmol) were added at RT. The reaction was stirred at 60 °C for 48 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain *tert*-butyl (4a*S*,8a*S*)-1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (0.120 g, 18.94% yield) as a solid. LCMS (Method G): Rt = 1.99 min, m/z = 829.8 $[M+H]^+$; 63.70%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetic acid



To a stirred solution of t*ert*-butyl (4a*S*,8a*S*)-1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (0.120 g, 0.142 mmol)) in DCM (2 mL) under a nitrogen atmosphere, TFA (0.044 mL, 0.569 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc (2 x 5 mL). The solvent was decanted, and the solid was dried under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetic acid (0.110 g, 94% yield) as a solid. LCMS (Method G): Rt = 1.58 min, m/z = 729.5 $[M+H]^+$; 77.01%. This material was used without further purification.

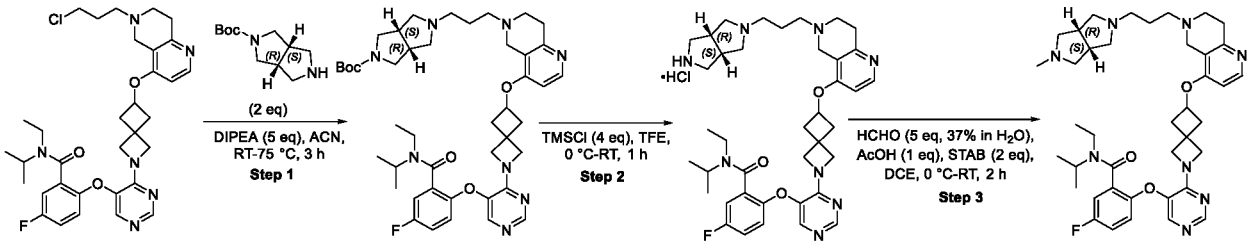
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-6-methyloctahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



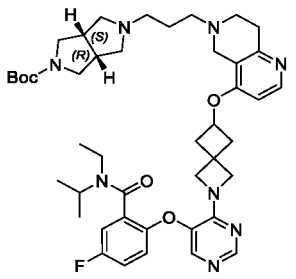
To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.120 g, 0.165 mmol) in dry DCE (4 mL), formaldehyde (0.668 mL, 8.23 mmol, 37% in H_2O) and AcOH (9.42 µL, 0.165 mmol) were added at 0 °C under a nitrogen atmosphere. The reaction was stirred at 0 °C for 2 h. To this solution, sodium triacetoxyborohydride (0.070 g, 0.329 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-6-methyloctahydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (23.13 mg, 18.69% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.81 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.81 - 3.70 (m, 2H), 4.60 - 3.51 (m, 1H), 3.47 - 3.36 (m, 3H), 3.27 - 3.20 (m, 1H), 3.18 - 3.09 (m, 2H), 2.83 - 2.72 (m, 10H), 2.72 - 2.64 (m, 2H), 2.30 - 2.17 (m, 3H), 2.15 (s, 3H), 2.13 - 2.07 (m, 1H), 1.96 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H), 1.68 - 1.54 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.70 min, m/z = 743.5 $[M+H]^+$; HPLC (Method A): Rt = 5.27 min, 98.81%; Chiral SFC (Method P): Rt = 1.56 min, 100%.

Example 205. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((3a*R*,6a*S*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 110)



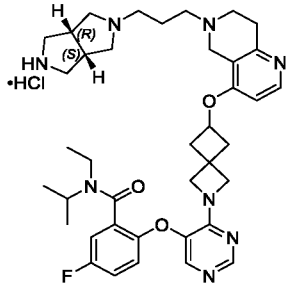
Step 1. tert-Butyl (3aR,6aS)-5-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 204, step 1, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of *tert*-butyl (3a*R*,6a*S*)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate was used. The reaction was stirred at 75 °C. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 70% EtOAc in hexane) to obtain *tert*-butyl (3a*R*,6a*S*)-5-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate.

Yield: 52.6%; LCMS (Method G): Rt = 2.20 min, m/z = 799.7 $[M+H]^+$, 81.95%.

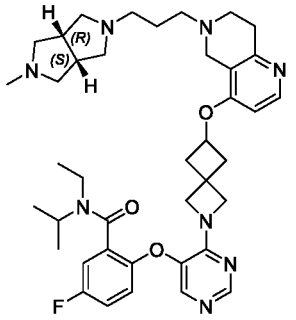
Step 2. N-Ethyl-5-fluoro-2-((4-(6-((6-(3-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 204, step 2, starting with *tert*-butyl (3a*R*,6a*S*)-5-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate, except that 4 equivalents of TMSCl was used, and TFE was used as a solvent. After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride as a viscous liquid.

Yield: 99%; LCMS (Method B): Rt = 0.25 min, m/z = 699.4 $[M+H]^+$, 50.90%. This material was used without further purification.

Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



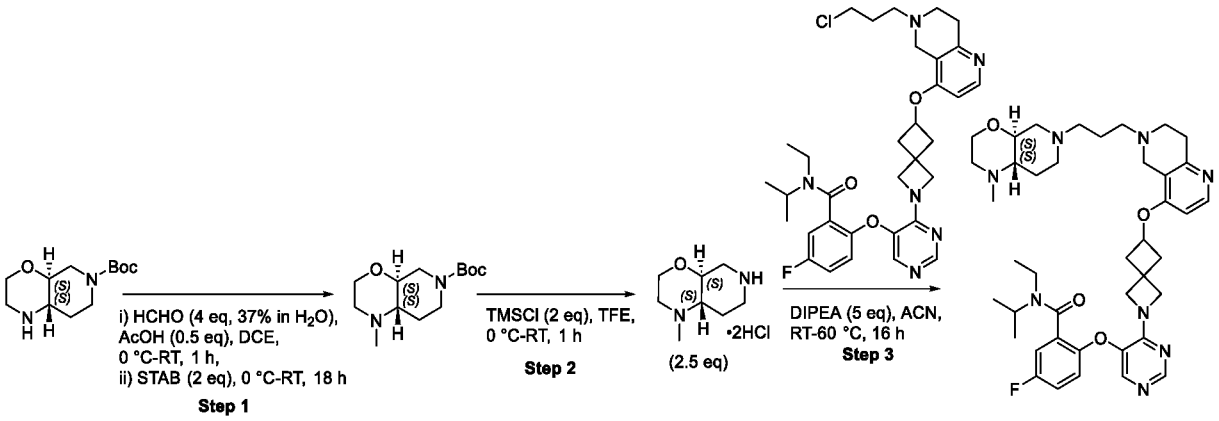
This compound was synthesized following the procedure described for the synthesis of Example 204, step 3, starting with *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride, except that 5 equivalents of formaldehyde (37 wt% in H_2O) was used. After completion, the reaction was quenched with 10% $NaHCO_3$ and extracted with 10% MeOH in DCM. The combined organic layer was dried under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((3a*R*,6a*S*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 9.85%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.80 - 4.71 (m, 1H), 4.32 - 4.06 (m, 4H), 3.75 (spt, J = 6.6 Hz, 1H), 3.45 - 3.38 (m, 3H), 3.26 - 3.11 (m, 2H), 2.84 - 2.75 (m, 4H), 2.70 - 2.66 (m, 2H), 2.54 - 2.60 (m, 4H), 2.48 - 2.41 (m, 3H), 2.40 - 2.32 (m, 2H), 2.31 - 2.11 (m, 9H), 1.64 (quin, J = 7.0 Hz, 2H), 1.31 - 0.90 (m, 9H); LCMS (Method A): Rt = 2.31 min, m/z = 713.6 $[M+H]^+$; HPLC (Method A): Rt = 4.75 min, 96.05%; Chiral SFC (Method P): Rt = 1.32 min, 100%.

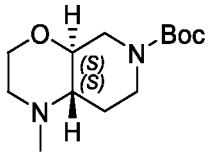
Example 206. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazin-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 111)

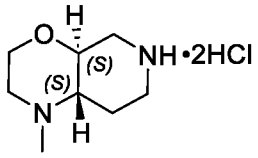


Step 1. tert-Butyl (4aS,8aS)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate



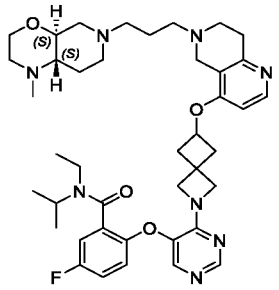
To a solution of *tert*-butyl (4a*S*, 8a*S*)-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (380 mg, 1.568 mmol) in DCE (10 mL), AcOH (0.045 mL, 0.784 mmol) and formaldehyde (0.467 mL, 6.27 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (665 mg, 3.14 mmol) was added at 0 °C. The reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, quenched with sodium bicarbonate solution, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80% EtOAc in hexane) to obtain *tert*-butyl (4a*S*, 8a*S*)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (240 mg, 52.0% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.93 (br s, 2H), 3.75 (dd, J = 2.4, 11.2 Hz, 1H), 3.60 (dt, J = 2.4, 11.5 Hz, 1H), 3.02 - 2.91 (m, 1H), 2.66 (d, J = 11.8 Hz, 2H), 2.20 (dt, J = 3.2, 11.7 Hz, 1H), 2.14 (s, 3H), 2.00 - 1.91 (m, 1H), 1.75 - 1.66 (m, 1H), 1.40 (s, 9H), 1.11 - 0.99 (m, 1H), one proton merged with solvent peak; LCMS (Method C): Rt = 1.66 min, m/z = 257.1 $[M+H]^+$; 87.13%.

Step 2. (4aS,8aS)-1-Methyloctahydro-1H-pyrido[3,4-b][1,4]oxazine dihydrochloride



To a solution of *tert*-butyl (4a*S*,8a*S*)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (0.24 g, 0.936 mmol) in 2,2,2-trifluoroethanol (2 mL) in a dried, 50 mL round bottom flask under a nitrogen atmosphere, TMSCl (0.239 mL, 1.872 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction was concentrated under reduced pressure to obtain crude (4a*S*,8a*S*)-1-methyloctahydro-1H-pyrido[3,4-b][1,4]oxazine dihydrochloride (0.14 g, 64.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (br s, 1H), 9.88 - 9.12 (m, 2H), 4.13 - 3.93 (m, 3H), 3.48 - 3.37 (m, 4H), 3.27 - 3.11 (m, 2H), 3.03 - 2.78 (m, 2H), 2.76 (br s, 3H), 2.44 - 2.35 (m, 1H), 2.01 - 1.89 (m, 1H); LCMS (Method B): Rt = 0.38 min, m/z = 157.2 $[M+H]^+$; 99.77%. This material was used without further purification.

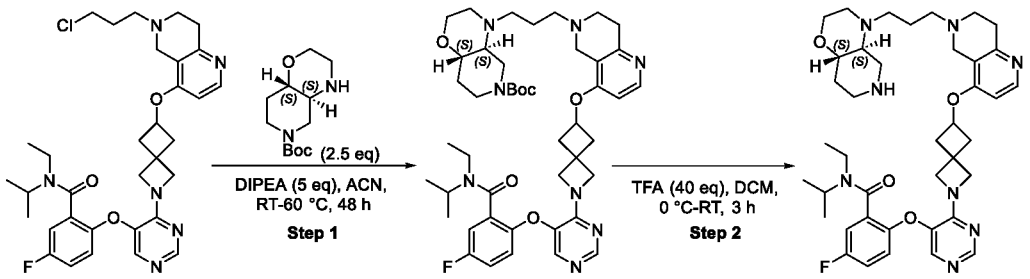
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazin-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



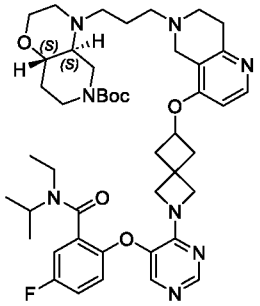
In a 20 mL pressure vial, 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.250 g, 0.401 mmol) in ACN (3 mL), (4a*S*,8a*S*)-1-methyloctahydro-1H-pyrido[3,4-b][1,4]oxazine dihydrochloride (0.138 g, 0.602 mmol) and DIPEA (0.349 mL, 2.006 mmol) were added. The reaction was stirred at 60 °C for 16 h. The reaction was concentrated under reduced pressure. The crude was diluted with ice-cold water (10 mL) and extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-1-methyloctahydro-6H-pyrido[3,4-b][1,4]oxazin-6-

yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (112.09 mg, 36.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.78 - 4.68 (m, 1H), 4.46 - 4.08 (m, 4H), 3.80 - 3.69 (m, 2H), 3.58 (td, J = 2.3, 11.4 Hz, 1H), 3.44 - 3.37 (m, 3H), 3.30 - 3.21 (m, 1H), 3.17 - 3.09 (m, 1H), 2.90 - 2.73 (m, 7H), 2.67 - 2.59 (m, 2H), 2.49 - 2.45 (m, 2H), 2.39 - 2.22 (m, 5H), 2.19 - 2.14 (m, 1H), 2.12 (s, 3H), 1.94 - 1.85 (m, 2H), 1.76 (t, J = 10.3 Hz, 1H), 1.64 (quin, J = 7.1 Hz, 2H), 1.55 - 1.48 (m, 1H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.63 min, m/z = 743.5 $[M+H]^+$; HPLC (Method A): Rt = 4.86 min, 98.24%; Chiral SFC (Method F): Rt = 1.92 min, 100%.

Example 207. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-octahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 107)



Step 1. tert-Butyl (4aS,8aS)-4-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate

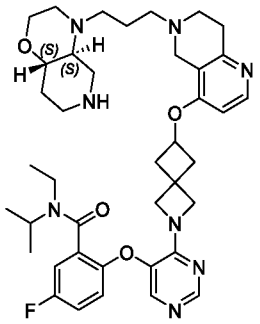


This compound was synthesized following the procedure described for the synthesis of Example 204, step 1, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2.5 equivalents of *tert*-butyl (4a*S*,8a*S*)-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage

isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (4a*S*,8a*S*)-4-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate as a solid.

Yield: 24.88%; LCMS (Method G): Rt = 2.07 min, m/z = 829.8 $[M+H]^+$, 96.20%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-octahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

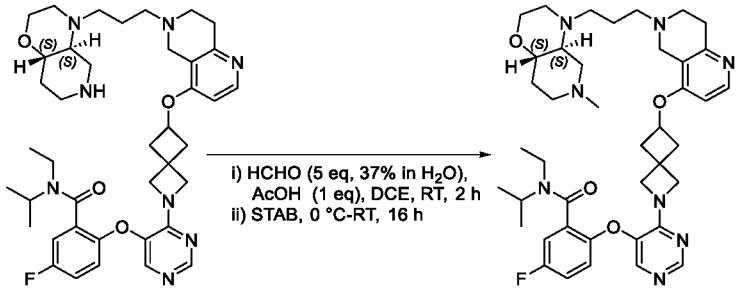


This compound was synthesized following the procedure described for the synthesis of Example204, step 2, starting with *tert*-butyl (4a*S*,8a*S*)-4-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate, except that 40 equivalents of TFA was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-octahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 77%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.20 - 8.15 (m, 1H), 7.78 - 7.65 (m, 1H), 7.35 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.72 - 6.63 (m, 1H), 4.81 - 4.68 (m, 1H), 4.46 - 4.05 (m, 4H), 3.80 - 3.69 (m, 2H), 3.64 - 3.51 (m, 1H), 3.47 - 3.35 (m, 4H), 3.29 - 3.11 (m, 1H), 3.09 - 2.99 (m, 1H), 2.93 - 2.82 (m, 1H), 2.81 - 2.72 (m, 4H), 2.70 - 2.64 (m, 2H), 2.46 - 2.39 (m, 4H), 2.31 - 2.16 (m, 3H), 2.15 - 2.01 (m, 3H), 1.91 - 1.75 (m, 1H), 1.73 - 1.46 (m, 4H), 1.45 - 1.24 (m, 1H), 1.22 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.55 min, m/z = 729.5 $[M+H]^+$; HPLC (Method A): Rt = 4.49 min, 96.61%; Chiral SFC (Method P): Rt = 1.91 min, 100%.

Example 208. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-6-methyloctahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 130)

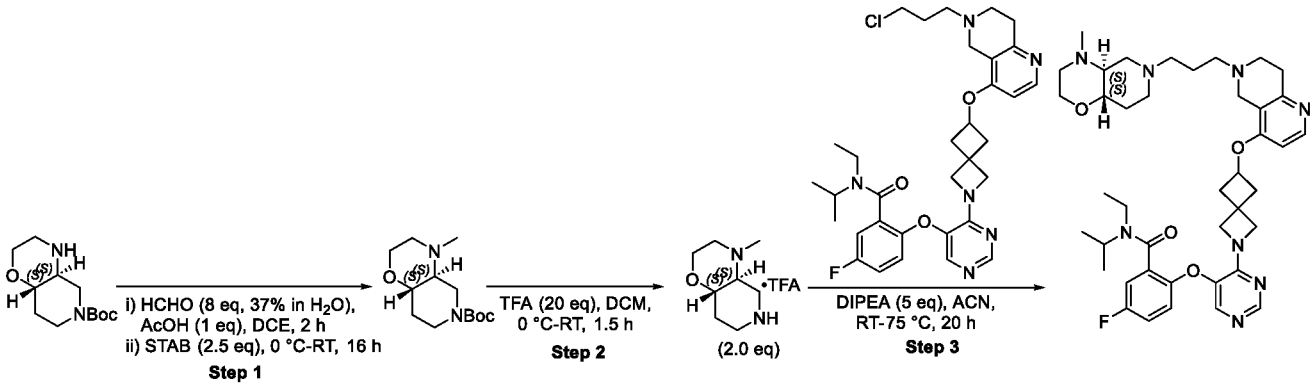


This compound was synthesized following the procedure described for the synthesis of Example 204, step 3, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-octahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 5 equivalents of formaldehyde (37% in H_2O) was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-6-methyloctahydro-4H-pyrido[4,3-b][1,4]oxazin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

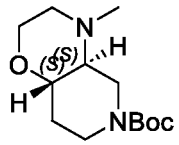
Yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 - 8.25 (m, 1H), 8.21 - 8.14 (m, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.20 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.63 (m, 1H), 4.81 - 4.67 (m, 1H), 4.33 - 4.07 (m, 4H), 3.80 - 3.69 (m, 2H), 3.59 - 3.49 (m, 1H), 3.46 - 3.35 (m, 3H), 3.28 - 3.11 (m, 1H), 3.08 - 3.00 (m, 1H), 3.00 - 2.89 (m, 1H), 2.84 - 2.61 (m, 7H), 2.50 - 2.44 (m, 6H), 2.37-2.33 (m, 1H), 2.31 - 2.17 (m, 3H), 2.14 (s, 3H), 2.03 - 1.86 (m, 2H), 1.71 - 1.36 (m, 3H), 1.24 - 0.91 (m, 9H); LCMS (Method G): Rt = 1.64 min, m/z = 743.5 $[M+H]^+$; HPLC (Method A): Rt = 4.62 min, 99.90%; Chiral SFC (Method F): Rt = 1.72 min, 100%.

Example 209. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazin-6(5H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 106)

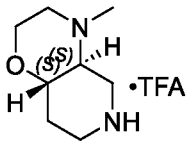


Step 1. tert-Butyl (4aS,8aS)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate



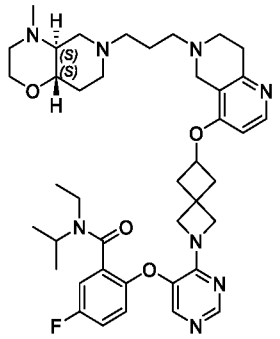
This compound was synthesized following the procedure described for the synthesis of Example 206, step 1, starting with 1 equivalent of *tert*-butyl (4a*S*,8a*S*)-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate, except that 8 equivalents of formaldehyde (37% in H_2O), 1 equivalent of AcOH, and 2.5 equivalents of STAB were used. The reaction was quenched with saturated sodium bicarbonate solution and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (4a*S*,8a*S*)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate as a solid. Yield: 96.63%; LCMS (Method C): Rt = 1.72 min, m/z = 257.1 $[M+H]^+$, 96.64%; This material was used without further purification.

Step 2. (4aS,8aS)-4-Methyloctahydro-2H-pyrido[4,3-b][1,4]oxazine trifluoroacetic acid



This compound was synthesized following the procedure described for the synthesis of Example 206, step 2, starting with *tert*-butyl (4a*S*,8a*S*)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate, except that 20 equivalents of TFA was used. The reaction was performed in DCM at 0 °C-RT for 1.5 h. The reaction was concentrated under reduced pressure to obtain crude (4a*S*,8a*S*)-4-methyloctahydro-2H-pyrido[4,3-b][1,4]oxazine trifluoroacetic acid (242 mg, 82% yield) as a semi-solid. This material was used without further purification.

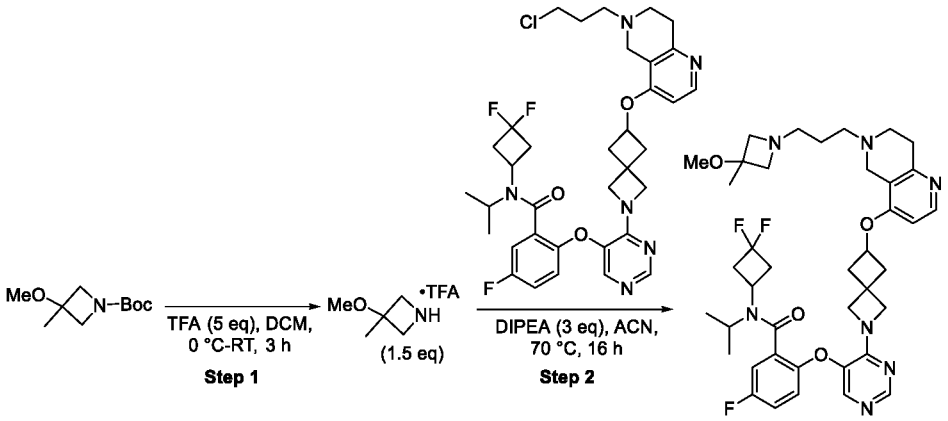
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-((4aS,8aS)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazin-6(5H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



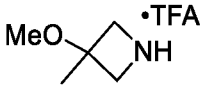
This compound was synthesized following the procedure described for the synthesis of Example 206, step 3, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of (4a*S*,8a*S*)-4-methyloctahydro-2H-pyrido[4,3-b][1,4]oxazine trifluoracetic acid was used. The reaction was stirred at 75 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-((4a*S*,8a*S*)-4-methylhexahydro-2H-pyrido[4,3-b][1,4]oxazin-6(5H)-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 30.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.35 - 7.20 (m, 2H), 7.11 - 6.97 (m, 1H), 6.66 (d, J = 5.7 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.33 - 4.05 (m, 4H), 3.83 - 3.68 (m, 2H), 3.60 - 3.52 (m, 1H), 3.46 - 3.34 (m, 2H), 3.30 - 3.20 (m, 2H), 3.15-3.11 (m, 1H), 3.02 - 2.92 (m, 1H), 2.88 - 2.74 (m, 5H), 2.71 - 2.65 (m, 3H), 2.63-2.60 (m, 1H), 2.48 - 2.43 (m, 2H), 2.41 - 2.31 (m, 1H), 2.30 - 2.22 (m, 1H), 2.20 - 2.13 (m, 1H), 2.12 (s, 3H), 1.95 (t, J = 11.3 Hz, 1H), 1.76 - 1.59 (m, 6H), 1.50 - 1.39 (m, 1H), 1.25 - 0.95 (m, 9H); LCMS (Method G): Rt = 1.57 min, m/z = 743.5 $[M+H]^+$; HPLC (Method A): Rt = 4.62 min, 97.86%; Chiral SFC (Method R): Rt = 1.52 min, 96.74%.

Example 210. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 262)

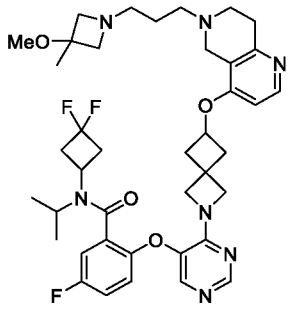


Step 1. 3-Methoxy-3-methylazetidine 2,2,2-trifluoroacetate



In a 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-methoxy-3-methylazetidine-1-carboxylate (350 mg, 1.739 mmol) was added in DCM (10 mL). TFA (0.665 mL, 8.69 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 3 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to afford crude 3-methoxy-3-methylazetidine 2,2,2-trifluoroacetate (300 mg, 80% yield) as a viscous liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 - 8.35 (m, 2H), 3.97 - 3.86 (m, 2H), 3.84 - 3.74 (m, 2H), 3.18 (s, 3H), 1.43 (s, 3H); LCMS (Method B): Rt = 0.32 min, m/z = 102.3 $[M+H]^+$, 99.90%. This material was used without further purification.

Step 2. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

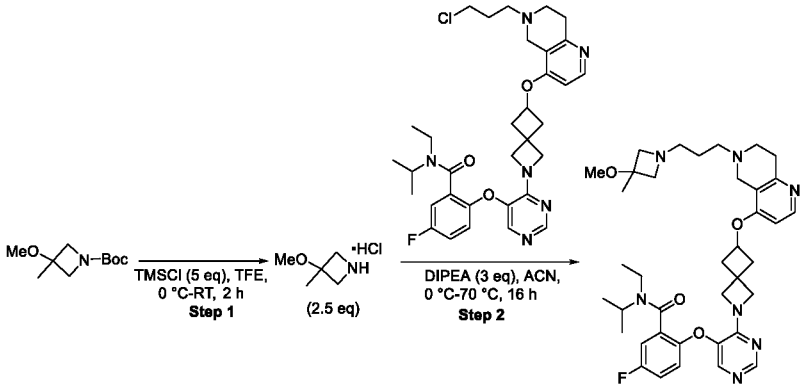


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 1.5 equivalents of 3-methoxy-3-methylazetidine 2,2,2-trifluoroacetate, except that 3 equivalents of DIPEA was used. The

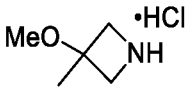
reaction was stirred at 70 °C. The crude was purified by Prep HPLC (Method C) to obtain *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 12.07%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, J = 5.8 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.33 (m, 1H), 7.32 - 7.23 (m, 1H), 7.07 (br d, J = 4.3 Hz, 1H), 6.66 (d, J = 5.8 Hz, 1H), 4.75 (br d, J = 6.6 Hz, 1H), 4.31 - 4.06 (m, 4H), 3.97 - 3.89 (m, 1H), 3.80 - 3.68 (m, 2H), 3.62 - 3.47 (m, 1H), 3.39 (s, 2H), 3.11 - 3.08 (m, 2H), 3.08 (s, 3H), 2.87 - 2.73 (m, 8H), 2.72 - 2.62 (m, 2H), 2.48 - 2.38 (m, 3H), 2.30 - 2.22 (m, 2H), 1.55 - 1.46 (m, 2H), 1.36 (s, 3H), 1.10 (d, J = 5.4 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H) one proton merged with solvent peaks; LCMS (Method G): Rt = 1.95 min, m/z = 750.7 $[M+H]^+$; HPLC (Method A): Rt = 5.63 min, 99.66%.

Example 211. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 293)

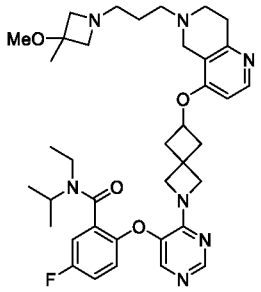


Step 1. 3-Methoxy-3-methylazetidine hydrochloride



In a 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-methoxy-3-methylazetidine-1-carboxylate (300 mg, 1.491 mmol) was added in TFE (5 mL). TMSCl (0.946 mL, 7.45 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude 3-methoxy-3-methylazetidine hydrochloride (200 mg, 96% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.62 - 8.99 (m, 2H), 3.94 - 3.81 (m, 2H), 3.79 - 3.68 (m, 2H), 3.17 (s, 3H), 1.45 (s, 3H); LCMS ELSD (Method G): Rt = 0.45 min, m/z = 102.3 $[M+H]^+$, 98.07%.

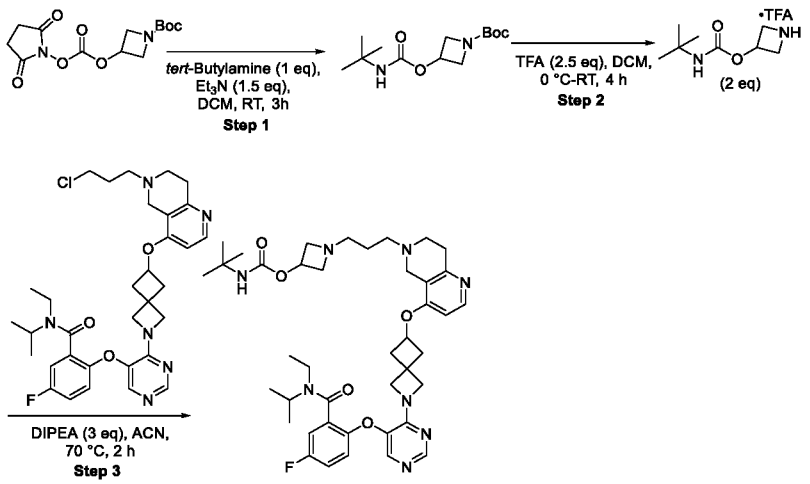
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



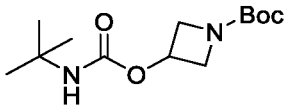
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2.5 equivalents of 3-methoxy-3-methylazetidine hydrochloride and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 47.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.24 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.35 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.70 - 6.62 (m, 1H), 4.83 - 4.69 (m, 1H), 4.34 - 4.07 (m, 4H), 3.81 - 3.70 (m, 1H), 3.46 - 3.37 (m, 3H), 3.29 - 3.14 (m, 1H), 3.12 - 3.10 (m, 1H), 3.08 (s, 4H), 2.89 - 2.73 (m, 6H), 2.70 - 2.62 (m, 2H), 2.49 - 2.38 (m, 4H), 2.31 - 2.22 (m, 2H), 1.50 (quin, J = 7.1 Hz, 2H), 1.36 (s, 3H), 1.24 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.85 min, m/z = 688.4 $[M+H]^+$; HPLC (Method A): Rt = 5.03 min, 97.50%.

Example 212. 1-(3-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-Fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl *tert*-butylcarbamate (Compound No. 220)

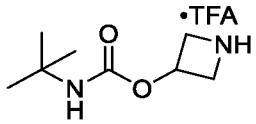


Step 1. tert-Butyl 3-((tert-butylcarbamoyl)oxy)azetidine-1-carboxylate



To a stirred solution of *tert*-butyl 3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)azetidine-1-carboxylate (450 mg, 1.432 mmol) in DCM (5 mL), Et_3N (0.299 mL, 2.148 mmol) and *tert*-butylamine (0.150 mL, 1.432 mmol) were added at RT. The reaction was stirred at the same temperature for 3 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with water (15 mL) and extracted with DCM (3 x 30 mL). The combined organic layer was washed with water (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 5-8% EtOAc in hexane) to afford *tert*-butyl 3-((*tert*-butylcarbamoyl)oxy)azetidine-1-carboxylate (170 mg, 43.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15 (s, 1 H), 5.01 - 4.93 (m, 1 H), 4.11 (t, J = 7.2 Hz, 2H), 3.75 - 3.60 (m, 2H), 1.38 (s, 9H), 1.21 (s, 9H).

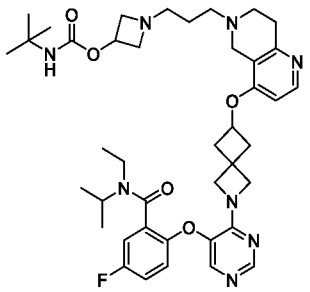
Step 2. Azetidin-3-yl tert-butylcarbamate 2,2,2-trifluoroacetate



To a stirred solution of *tert*-butyl 3-((*tert*-butylcarbamoyl)oxy)azetidine-1-carboxylate (100 mg, 0.367 mmol) in DCM (0.5 mL), TFA (0.070 mL, 0.918 mmol) was added at 0 °C, and the reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to afford crude azetidin-3-yl *tert*-butylcarbamate 2,2,2-trifluoroacetate (90 mg, 86% yield) as a viscous liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 - 8.54 (m, 2H), 7.29 (s,

1H), 5.08 (quin, *J* = 6.3 Hz, 1H), 4.30 - 4.18 (m, 4H), 1.22 (s, 9H). This material was used without further purification.

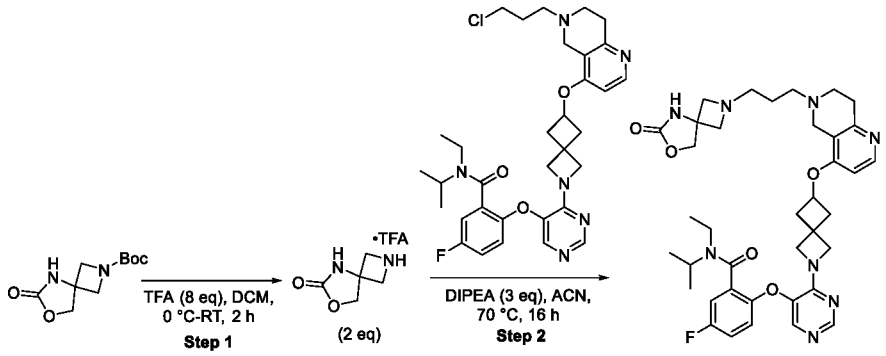
Step 3. 1-(3-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl tert-butylcarbamate



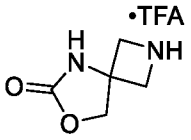
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of azetidin-3-yl *tert*-butylcarbamate 2,2,2-trifluoroacetate and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl *tert*-butylcarbamate as a solid.

Yield: 18.60%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 - 8.15 (m, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.12 - 6.95 (m, 2H), 6.70 - 6.63 (m, 1H), 4.84 - 4.69 (m, 2H), 4.31 - 4.06 (m, 4H), 3.80 - 3.71 (m, 1H), 3.57 - 3.49 (m, 2H), 3.46 - 3.36 (m, 3H), 3.28 - 3.10 (m, 1H), 2.87 - 2.73 (m, 6H), 2.71 - 2.62 (m, 2H), 2.47 - 2.38 (m, 4H), 2.32 - 2.18 (m, 2H), 1.56 - 1.45 (m, 2H), 1.20 (s, 9H), 1.15 - 0.98 (m, 9H); LCMS (Method G): Rt = 1.86 min, m/z = 759.7 $[M+H]^+$, 98.11%; HPLC (Method A): Rt = 5.51 min, 97.71%.

Example 213. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 236)

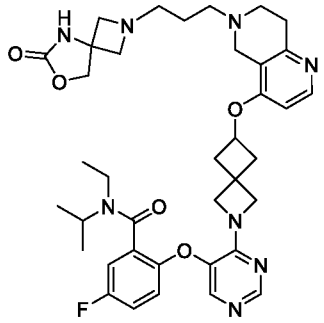


Step 1. 7-Oxa-2,5-diazaspiro[3.4]octan-6-one 2,2,2-trifluoroacetate



In a 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate (0.15 g, 0.657 mmol) was added in DCM (4 mL). TFA (0.405 mL, 5.26 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude 7-oxa-2,5-diazaspiro[3.4]octan-6-one 2,2,2-trifluoroacetate (0.145 g, 98% yield) as a viscous liquid. LCMS (Method B): Rt = 0.28 min, m/z = 129.3 $[M+H]^+$, 99.91%. This material was used without further purification.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

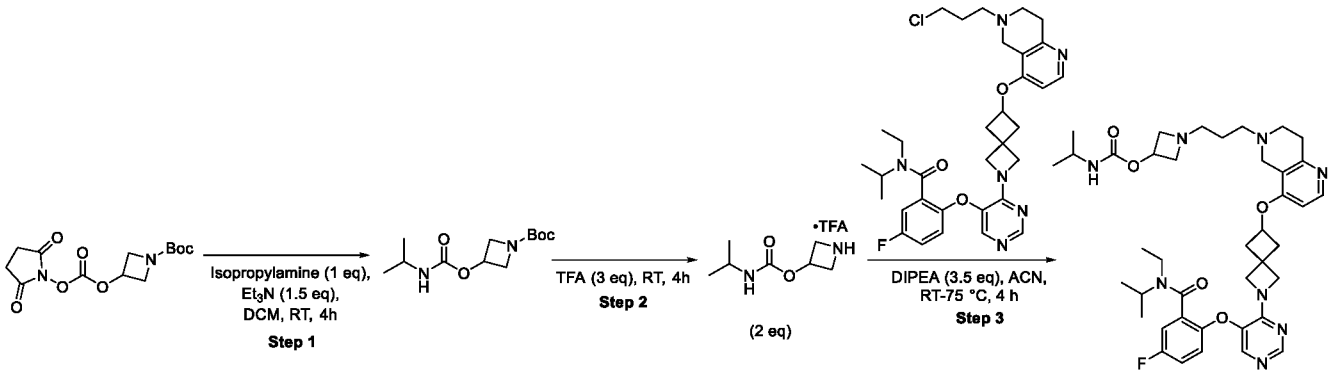


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 7-oxa-2,5-diazaspiro[3.4]octan-6-one 2,2,2-trifluoroacetate and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C. After completion, the reaction was concentrated under reduced pressure. The crude was

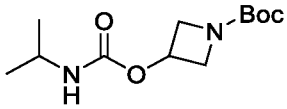
purified by Prep HPLC (Method W) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 15.93%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.27 - 8.25 (m, 1H), 8.20 - 8.15 (m, 1H), 7.77 - 7.66 (m, 1H), 7.35 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.71 (m, 1H), 4.45 (s, 2H), 4.31 - 4.07 (m, 4H), 3.81 - 3.71 (m, 1H), 3.45 - 3.37 (m, 5H), 3.29 - 3.11 (m, 2H), 3.06 - 3.00 (m, 2H), 2.83 - 2.73 (m, 4H), 2.70 - 2.62 (m, 2H), 2.46 (t, *J* = 7.3 Hz, 1H), 2.42 - 2.32 (m, 2H), 2.30 - 2.21 (m, 2H), 1.55 - 1.44 (m, 2H), 1.24 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.58 min, m/z = 715.7 $[M+H]^+$; HPLC (Method A): Rt = 4.61 min, 99.89%.

Example 214. 1-(3-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-Azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl isopropylcarbamate (Compound No. 256)



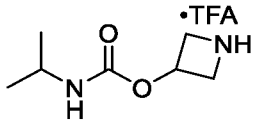
Step 1. tert-Butyl 3-((isopropylcarbamoyl)oxy)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 212, step 1, starting with *tert*-butyl 3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)azetidine-1-carboxylate, except that 1 equivalent of isopropyl amine was used. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 10% EtOAc in hexane) to afford *tert*-butyl 3-((isopropylcarbamoyl)oxy)azetidine-1-carboxylate as a solid.

Yield: 38.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 (d, *J* = 7.5 Hz, 1H), 5.04 - 4.95 (m, 1H), 4.19 - 4.08 (m, 2H), 3.77 - 3.64 (m, 2H), 3.63 - 3.51 (m, 1H), 1.38 (s, 9H), 1.05 (d, *J* = 6.5 Hz, 6H).

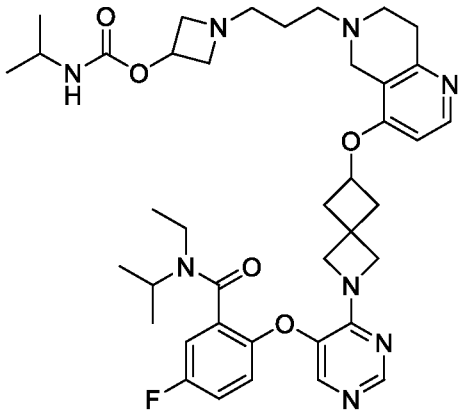
Step 2. Azetidin-3-yl isopropylcarbamate 2,2,2-trifluoroacetate



This compound was synthesized following the procedure described for the synthesis of Example 212, step 2, starting with *tert*-butyl 3-((isopropylcarbamoyl)oxy)azetidine-1-carboxylate, except that 3 equivalents of TFA was used. The crude was triturated with MTBE to obtain azetidin-3-yl isopropylcarbamate 2,2,2-trifluoroacetate as a solid.

Yield: 100%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 - 8.54 (m, 2H), 7.43 (br d, J = 7.8 Hz, 1H), 5.15 - 5.04 (m, 1H), 4.27 - 4.17 (m, 3H), 4.00 - 3.84 (m, 2H), 3.58 (quin, J = 6.7 Hz, 1H), 1.06 (d, J = 6.6 Hz, 6H)

Step 3. 1-(3-(4-((2-(5-(2-(Ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-Azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl isopropylcarbamate

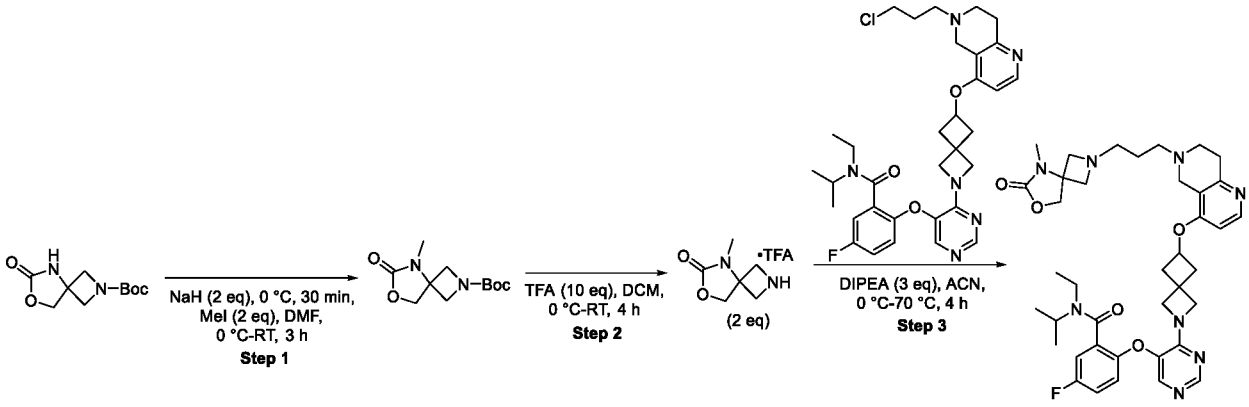


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of azetidin-3-yl isopropylcarbamate 2,2,2-trifluoroacetate and 3.5 equivalents of DIPEA were used. The reaction was stirred at 75 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl isopropylcarbamate as a solid.

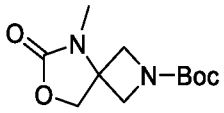
Yield: 10.34%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 - 8.15 (m, 1H), 7.77 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.14 (br d, J = 7.5 Hz, 1H), 7.11 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.87 - 4.70 (m, 2H), 4.32 - 4.07 (m, 4H), 3.76 (quin, J = 6.7 Hz, 1H),

3.62 - 3.48 (m, 3H), 3.45 - 3.36 (m, 3H), 3.29 - 3.09 (m, 2H), 2.89 - 2.73 (m, 5H), 2.71 - 2.61 (m, 2H), 2.48 - 2.36 (m, 4H), 2.32 - 2.21 (m, 2H), 1.50 (quin, *J* = 7.0 Hz, 2H), 1.27 - 0.94 (m, 15H); LCMS (Method G): Rt = 1.93 min, m/z = 745.4 $[M+H]^+$; HPLC (Method A): Rt = 5.27 min, 99.51%.

Example 215. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 257)

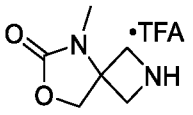


Step 1. tert-Butyl 5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate



To a stirred solution of *tert*-butyl 6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate (300 mg, 1.314 mmol) in DMF (8 mL), sodium hydride (105 mg, 2.63 mmol) was added at 0 °C. The reaction was stirred at the same temperature for 30 min. To this reaction mixture, methyl iodide (0.164 mL, 2.63 mmol) was added at 0 °C, and the reaction was stirred for 3 h at RT. The reaction progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 45 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was triturated with MTBE (3 x 10 mL) to afford *tert*-butyl 5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate (200 mg, 62.8% yield) as a solid. LCMS (Method G): Rt = 1.46 min, m/z = 243.2 $[M+H]^+$, 66.59%.

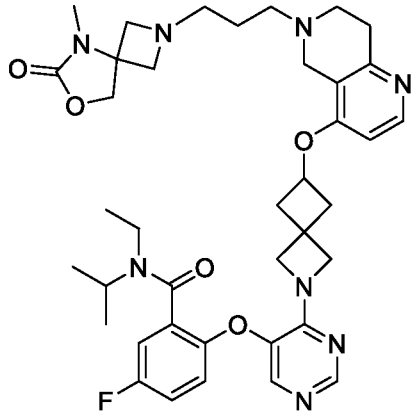
Step 2. 5-Methyl-7-oxa-2,5-diazaspiro[3.4]octan-6-one 2,2,2-trifluoroacetate



To a stirred solution of *tert*-butyl 5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octane-2-carboxylate (200 mg, 0.826 mmol) in DCM (0.5 mL), trifluoroacetic acid (0.636 mL, 8.26

mmol) was added at 0 °C. The reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC(10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was triturated with MTBE (3 x 15 mL) to afford 5-methyl-7-oxa-2,5-diazaspiro[3.4]octan-6-one 2,2,2-trifluoroacetate (206 mg, 97% yield) as a solid. LCMS (Method B): Rt = 0.28 min, m/z = 143.3 $[M+H]^+$, 99.70%.

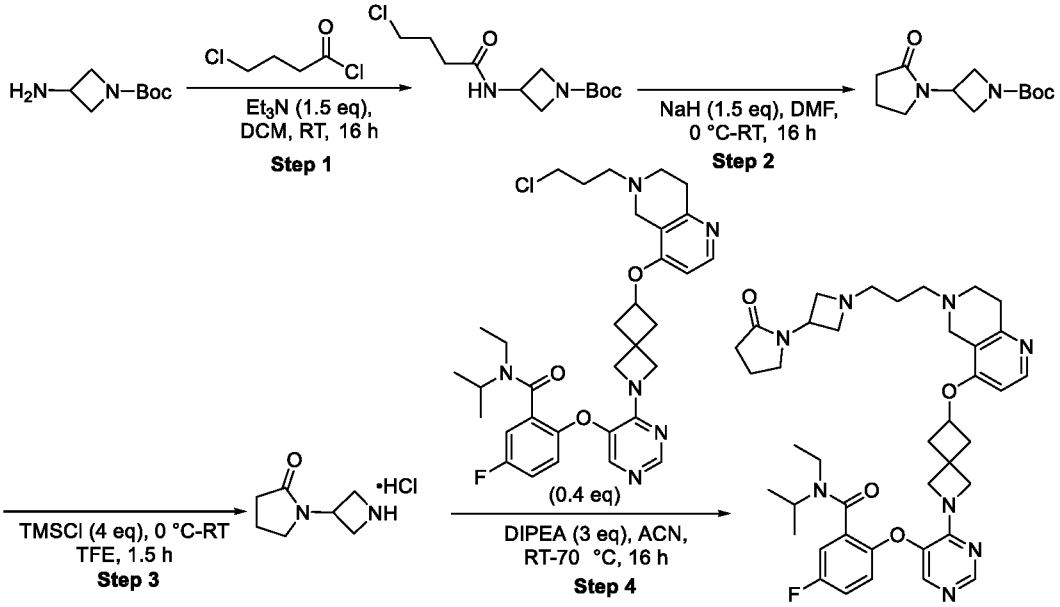
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



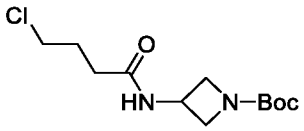
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 5-methyl-7-oxa-2,5-diazaspiro[3.4]octan-6-one 2,2,2-trifluoroacetate and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(5-methyl-6-oxo-7-oxa-2,5-diazaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 9.43%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.66 (br d, J = 6.0 Hz, 1H), 4.77 - 4.70 (m, 1H), 4.40 (s, 2H), 4.31 - 4.07 (m, 4H), 3.80 - 3.71 (m, 1H), 3.43 - 3.37 (m, 5H), 3.28 - 3.10 (m, 4H), 2.87 (s, 3H), 2.83 - 2.76 (m, 3H), 2.70 - 2.63 (m, 3H), 2.45 - 2.37 (m, 3H), 2.31 - 2.21 (m, 2H), 1.56 - 1.45 (m, 2H), 1.27 - 0.93 (m, 9H); LCMS (Method G): Rt = 1.66 min, m/z = 729.5 $[M+H]^+$; HPLC (Method A): Rt = 4.84 min, 99.73%.

Example 216. ***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-(2-oxopyrrolidin-1-yl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 221)

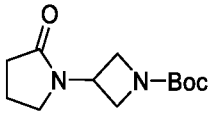


Step 1. tert-Butyl 3-(4-chlorobutanamido)azetidine-1-carboxylate



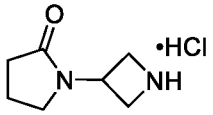
To a stirred solution of *tert*-butyl 3-aminoazetidine-1-carboxylate (0.5 g, 2.90 mmol) in DCM (15 mL), Et_3N (0.607 mL, 4.35 mmol) was added at 0 °C. 4-Chlorobutanoyl chloride (0.409 g, 2.90 mmol) was added to this reaction mixture. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to 0 °C, quenched with water (25 mL), and extracted with DCM (3 x 25 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain *tert*-butyl 3-(4-chlorobutanamido)azetidine-1-carboxylate (800 mg, 94% yield) as an oil. ^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (d, J = 6.9 Hz, 1H), 4.43 - 4.34 (m, 1H), 4.04 (t, J = 8.1 Hz, 2H), 3.70 - 3.60 (m, 4H), 2.24 (t, J = 7.3 Hz, 2H), 2.00 - 1.87 (m, 2H), 1.38 (m, 9H); LCMS (Method G): Rt = 1.56 min, m/z = 277.2 $[M+H]^+$, 94.40%.

Step 2. tert-Butyl 3-(2-oxopyrrolidin-1-yl)azetidine-1-carboxylate



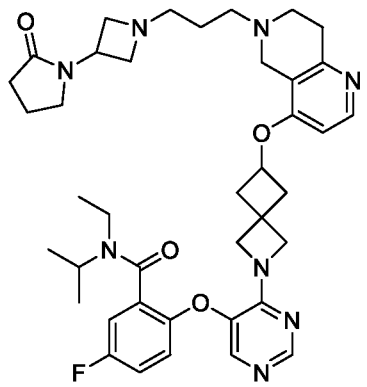
To a stirred solution of *tert*-butyl 3-(4-chlorobutanamido)azetidine-1-carboxylate (0.6 g, 2.168 mmol) in DMF (15 mL) under a nitrogen atmosphere, sodium hydride (0.078 g, 3.25 mmol) was added portion-wise at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with ice-cold water (25 mL), and extracted with DCM (3 x 25 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 70% EtOAc in hexane) to obtain *tert*-butyl 3-(2-oxopyrrolidin-1-yl)azetidine-1-carboxylate (500 mg, 94% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 - 4.96 (m, 1H), 4.16 (t, *J* = 8.9 Hz, 2H), 4.02 - 3.95 (m, 2H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.44 (t, *J* = 8.1 Hz, 2H), 2.15 - 2.07 (m, 2H), 1.47 (s, 9H); LCMS (Method I): Rt = 1.92 min, m/z = 141.1 [M-100]$^+$, 98.16%.

Step 3. 1-(Azetidin-3-yl)pyrrolidin-2-one hydrochloride



In a 100 mL single neck round bottom flask under a nitrogen atmosphere, *tert*-butyl 3-(2-oxopyrrolidin-1-yl)azetidine-1-carboxylate (300 mg, 1.248 mmol) was dissolved in 2,2,2-trifluoroethanol (10 mL). TMSCl (638 mL, 4.99 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 1.5 h. The progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude 1-(azetidin-3-yl)pyrrolidin-2-one hydrochloride (250 mg, quantitative yield) as a solid. This material was used without further purification.

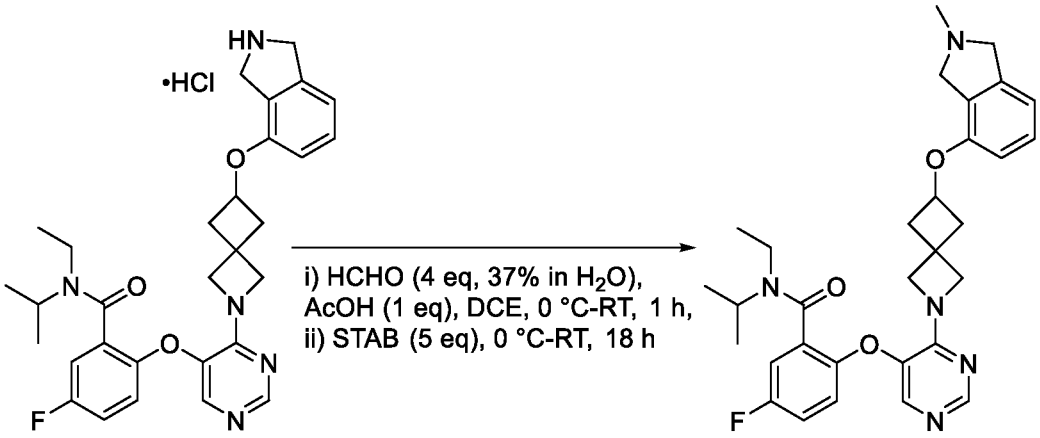
Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(3-(2-oxopyrrolidin-1-yl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 0.4 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of 1-(azetidin-3-yl)pyrrolidin-2-one hydrochloride and 3 equivalents of DIPEA were used. The reaction was stirred at 70 °C. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by Prep HPLC (Method AT) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(3-(2-oxopyrrolidin-1-yl)azetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

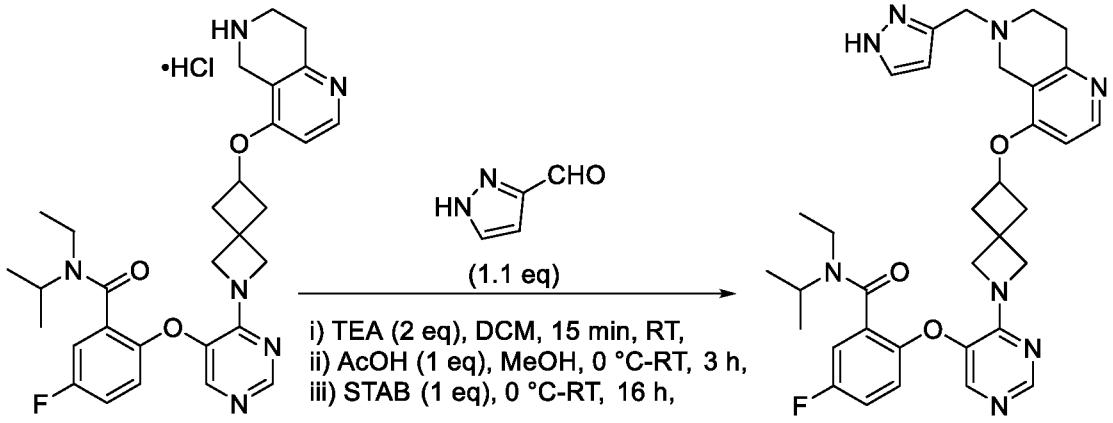
Yield: 9.06%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.21 - 8.15 (m, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.79 - 4.68 (m, 1H), 4.54 - 4.39 (m, 1H), 4.30 - 4.07 (m, 4H), 3.80 - 3.71 (m, 1H), 3.47 (t, J = 7.0 Hz, 2H), 3.42 - 3.36 (m, 6H), 3.27 - 3.19 (m, 2H), 3.03 (t, J = 7.3 Hz, 2H), 2.82 - 2.74 (m, 4H), 2.69 - 2.66 (m, 2H), 2.43 - 2.38 (m, 2H), 2.29 - 2.19 (m, 4H), 1.97 - 1.88 (m, 2H), 1.55 - 1.46 (m, 2H), 1.16 - 0.97 (m, 9H); LCMS (Method I): Rt = 2.00 min, m/z = 727.3 $[M+H]^+$; HPLC (Method A): Rt = 4.67 min, 98.79%.

Example 217. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 22)



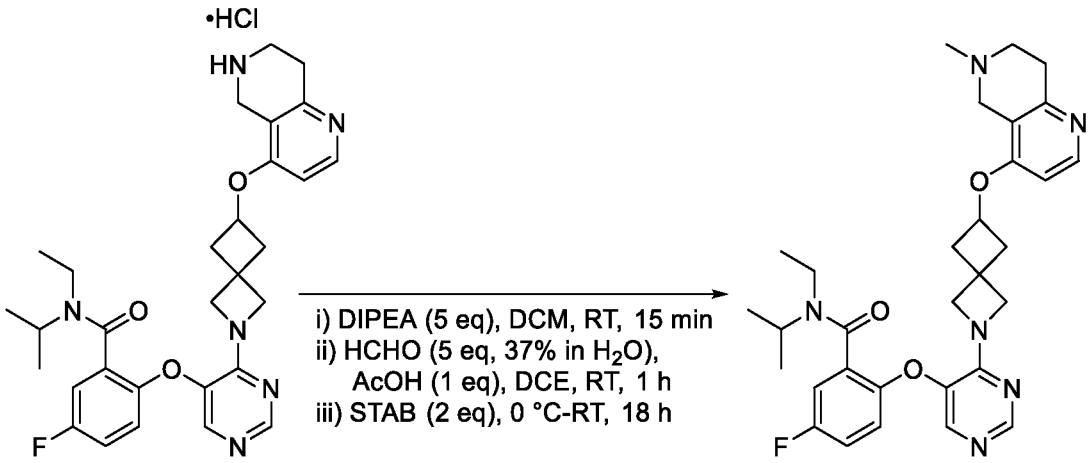
In a 50 mL round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride (250 mg, 0.440 mmol) was added in DCE (10 mL). To this solution, formaldehyde (0.131 mL, 1.760 mmol, 37% in H_2O) and acetic acid (0.025 mL, 0.440 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. To this reaction, sodium triacetoxyborohydride (466 mg, 2.200 mmol) was added at 0 °C, and the reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was quenched with water (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method J). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (112.45 mg, 46.7%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 - 8.24 (m, 1H), 7.79 - 7.64 (m, 1H), 7.37 - 7.18 (m, 2H), 7.15 - 6.98 (m, 2H), 6.80 (d, J = 7.4 Hz, 1H), 6.66 - 6.60 (m, 1H), 4.70 - 4.58 (m, 1H), 4.31 - 4.07 (m, 4H), 3.86 - 3.69 (m, 5H), 3.45 - 3.36 (m, 1H), 3.28 - 3.10 (m, 1H), 2.82 - 2.69 (m, 2H), 2.45 (s, 3H), 2.29 - 2.13 (m, 2H), 1.26 - 1.00 (m, 9H); LCMS (Method B): Rt = 1.28 min, m/z = 546.2 $[M+H]^+$; HPLC (Method A): Rt = 5.94 min, 99.62%.

Example 218. 2-((4-(6-((6-((1H-Pyrazol-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 87)



In a dried, 50 mL round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (250 mg, 0.429 mmol) was added in DCM (3 mL). Et_3N (0.115 mL, 0.857 mmol) was added to this solution at 0 °C, and the reaction was stirred for 15 min at RT. The reaction was concentrated under reduced pressure. To this crude material, MeOH (5 mL) was added, and then 1H-pyrazole-3-carbaldehyde (45.3 mg, 0.472 mmol) and AcOH (25.7 mg, 0.429 mmol) were added at 0 °C. The reaction was stirred at RT for 3 h. To this reaction, sodium triacetoxyborohydride (91 mg, 0.429 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM) and LCMS. The reaction was diluted with water (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain 2-((4-(6-((6-((1H-pyrazol-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (19.01 mg, 6.83% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 - 12.48 (m, 1H), 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.77 - 7.62 (m, 2H), 7.34 - 7.23 (m, 2H), 7.11 - 6.98 (m, 1H), 6.66 (d, J = 5.7 Hz, 1H), 6.18 (s, 1H), 4.76 - 4.68 (m, 1H), 4.33 - 4.08 (m, 4H), 3.80 - 3.64 (m, 3H), 3.46 (s, 2H), 3.43 - 3.37 (m, 1H), 3.28 - 3.13 (m, 1H), 2.85 - 2.70 (m, 6H), 2.31 - 2.18 (m, 2H), 1.21 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.48 min, m/z = 627.4 $[M+H]^+$; HPLC (Method A): Rt = 4.88 min, 96.71%.

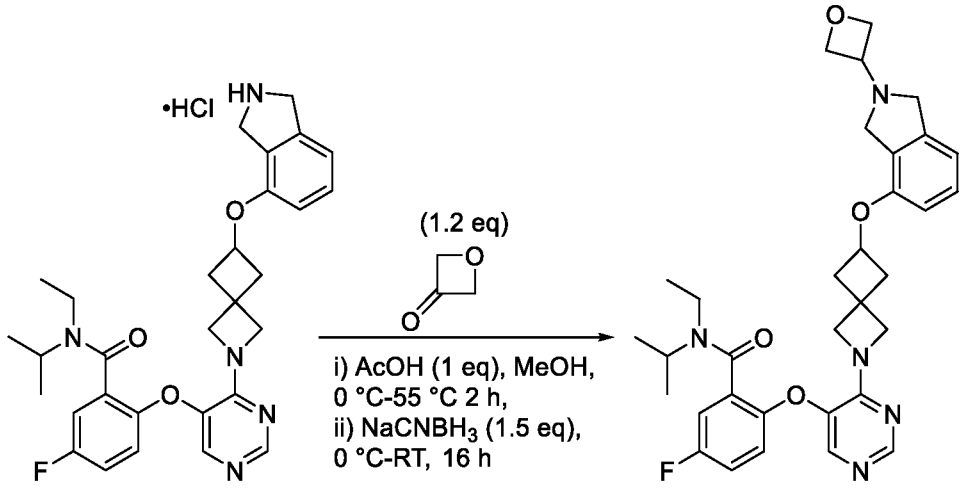
Example 219. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 59)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 5 equivalents of formaldehyde (37% in H_2O), 5 equivalents of DIPEA, and 2 equivalents of STAB were used, and DCE was used as the solvent. After completion, the reaction was quenched with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by Prep HPLC (Method AF) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

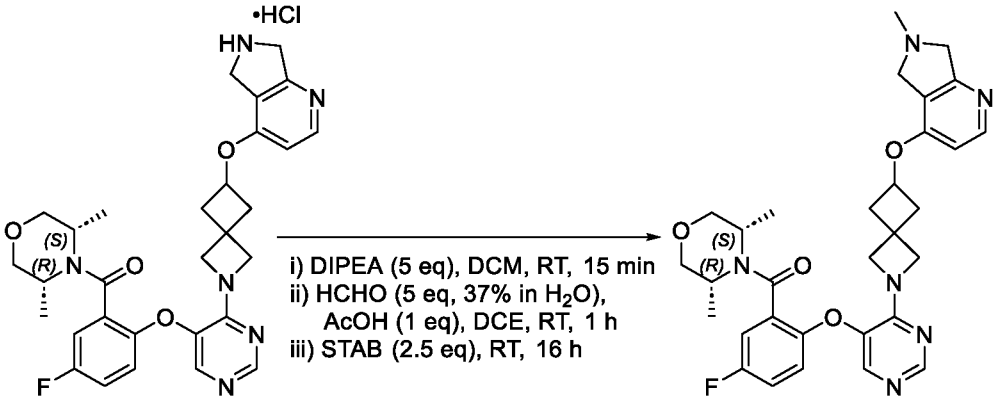
Yield: 27.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.79 - 7.63 (m, 1H), 7.36 - 7.20 (m, 2H), 7.12 - 6.98 (m, 1H), 6.71 - 6.62 (m, 1H), 4.81 - 4.69 (m, 1H), 4.34 - 4.05 (m, 4H), 3.75 (spt, J = 6.6, 13.1 Hz, 1H), 3.44 - 3.35 (m, 3H), 3.27 - 3.14 (m, 1H), 2.86 - 2.70 (m, 4H), 2.62 (t, J = 5.8 Hz, 2H), 2.36 (s, 3H), 2.31 - 2.20 (m, 2H), 1.34 - 0.89 (m, 9H); LCMS (Method B): Rt = 1.37 min, m/z = 561.3 $[M+H]^+$; HPLC (Method A): Rt = 5.19 min, 99.92%.

Example 220. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-(oxetan-3-yl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 28)



To a stirred solution of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride (200 mg, 0.352 mmol) and oxetan-3-one (30.4 mg, 0.422 mmol) in MeOH (5 mL), AcOH (0.02 mL, 0.352 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred at 55 °C for 2 h. To this reaction, sodium cyanoborohydride (33.2 mg, 0.528 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was poured into water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method A). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((2-(oxetan-3-yl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (75.42 mg, 35.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.23 (m, 1H), 7.79 - 7.64 (m, 1H), 7.37 - 7.21 (m, 2H), 7.18 - 6.99 (m, 2H), 6.83 (d, J = 7.4 Hz, 1H), 6.68 - 6.63 (m, 1H), 4.70 - 4.53 (m, 5H), 4.30 - 4.07 (m, 4H), 3.95 (quin, J = 6.2 Hz, 1H), 3.87 (s, 2H), 3.81 (s, 2H), 3.80 - 3.70 (m, 1H), 3.45 - 3.36 (m, 1H), 3.27 - 3.11 (m, 1H), 2.81 - 2.69 (m, 2H), 2.27 - 2.17 (m, 2H), 1.22 - 1.00 (m, 9H); LCMS (Method D): Rt = 1.89 min, m/z = 588.5 $[M+H]^+$; HPLC (Method A): Rt = 5.72 min, 96.84%.

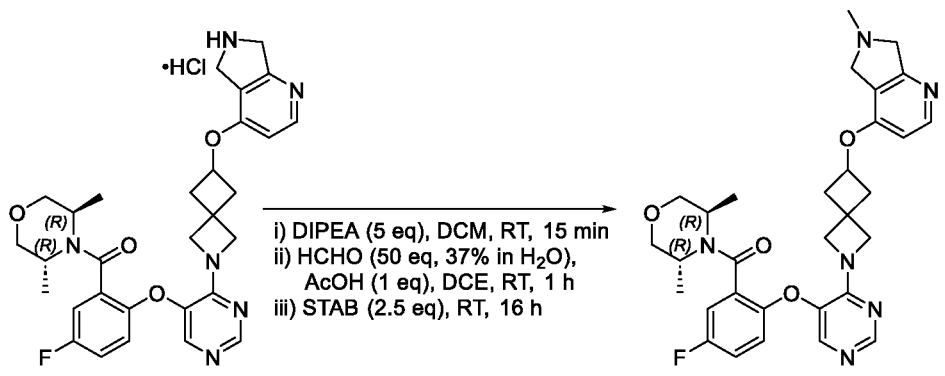
Example 221. ((3*S*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 35)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3S,5R)-3,5-dimethylmorpholino)methanone hydrochloride and 5 equivalents of formaldehyde (37% in H_2O), except that 5 equivalents of DIPEA and 2.5 equivalents of STAB were used, and DCE was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain pure ((*3S,5R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (0.06 g, 47.5% yield) as a solid.

Yield: 47.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.19 (d, J = 5.8 Hz, 1H), 7.83 - 7.70 (m, 1H), 7.43 - 7.32 (m, 1H), 7.31 - 7.23 (m, 1H), 7.11 - 6.97 (m, 1H), 6.71 (d, J = 5.9 Hz, 1H), 4.83 - 4.71 (m, 1H), 4.45 - 4.03 (m, 4H), 3.78 (br s, 4H), 3.74- 3.53 (m, 4H), 2.85 - 2.71 (m, 2H), 2.54 - 2.52 (m, 2H), 2.47 (s, 3H), 2.30 - 2.21 (m, 2H), 1.31 - 1.13 (m, 6H); LCMS (Method D): Rt = 1.55 min, m/z = 575.3 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 99.69%; Chiral SFC (Method H): Rt 3.53 min, 100%.

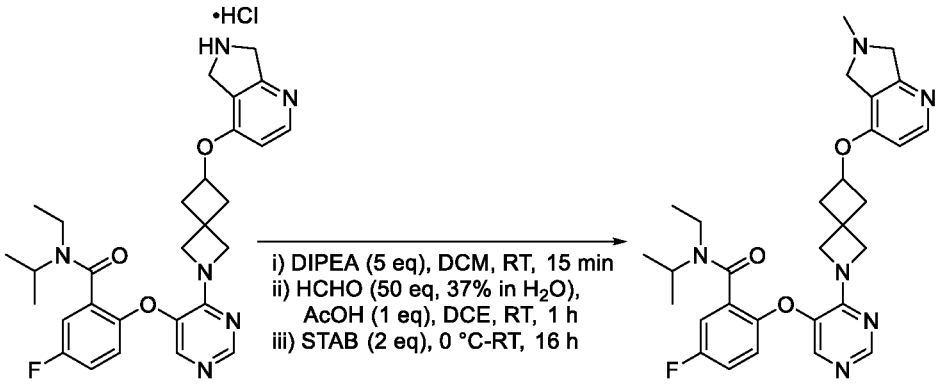
Example 222. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 30)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone hydrochloride and 50 equivalents of formaldehyde(37% in H_2O), except that 5 equivalents of DIPEA and 2.5 equivalents of STAB were used, and DCE was used as a solvent. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (0.15 g, 61.3% yield) as a solid.

Yield: 61.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.19 (d, J = 5.8 Hz, 1H), 7.70 (s, 1H), 7.43 - 7.34 (m, 1H), 7.33 - 7.26 (m, 1H), 7.07-7.02 (m, 1H), 6.71 (d, J = 5.8 Hz, 1H), 4.84-4.72 (m, 1H), 4.23 (br s, 2H), 4.16 (br s, 2H), 4.01 - 3.83 (m, 2H), 3.80 - 3.75 (m, 4H), 3.75 - 3.61 (m, 2H), 2.84 - 2.75 (m, 2H), 2.58 - 2.52 (m, 2H), 2.47 (s, 3H), 2.31 - 2.22 (m, 2H), 1.19 (br s, 6H); LCMS (Method B): Rt = 1.46 min, m/z = 575.6 $[M+H]^+$; HPLC (Method D): Rt = 2.27 min, 98.02%; Chiral SFC (Method H): Rt 3.88 min, 100%.

Example 223. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 27)

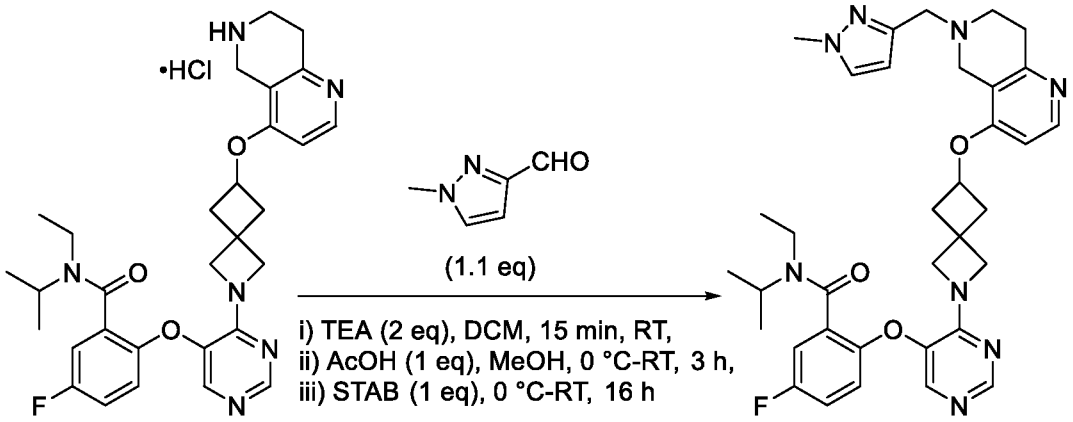


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 5 equivalents of DIPEA and 2 equivalents of STAB were used, and DCE was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B:

ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.21 - 8.18 (m, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.19 (m, 2H), 7.11 - 7.00 (m, 1H), 6.73 - 6.72 (m, 1H), 4.85 - 4.73 (m, 1H), 4.32 - 4.06 (m, 4H), 3.78 (br s, 2H), 3.76 - 3.73 (m, 4H), 3.48 - 3.38 (m, 1H), 2.84 - 2.73 (m, 2H), 2.47 (s, 3H), 2.32 - 2.19 (m, 2H), 1.22 - 0.97 (m, 9H). LCMS (Method B): Rt = 1.54 min, m/z = 547.6 $[M+H]^+$; HPLC (Method D): Rt = 2.44 min, 97.85%.

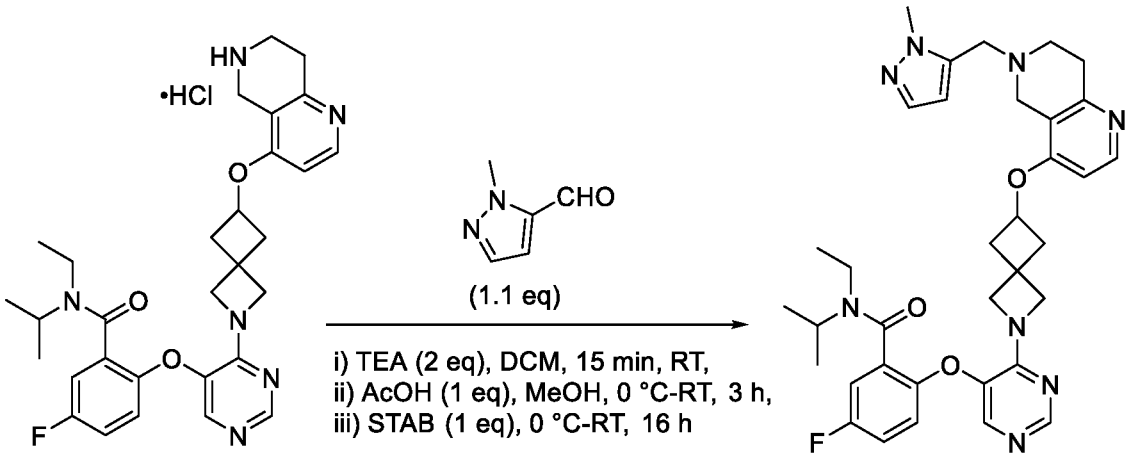
Example 224. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 93)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.1 equivalents of 1-methyl-1H-pyrazole-3-carbaldehyde was used. The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 17.38%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.34 - 7.20 (m, 2H), 7.12 - 7.00 (m, 1H), 6.68 - 6.62 (m, 1H), 6.15 (d, J = 2.1 Hz, 1H), 4.78 - 4.68 (m, 1H), 4.46 - 4.06 (m, 4H), 3.80 (s, 3H), 3.77 - 3.71 (m, 1H), 3.63 (s, 2H), 3.46 (s, 2H), 3.43 - 3.37 (m, 1H), 3.27 - 3.15 (m, 1H), 2.82 - 2.68 (m, 6H), 2.28 - 2.18 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.60 min, m/z = 641.7 $[M+H]^+$; HPLC (Method A): Rt = 5.06 min, 97.54%.

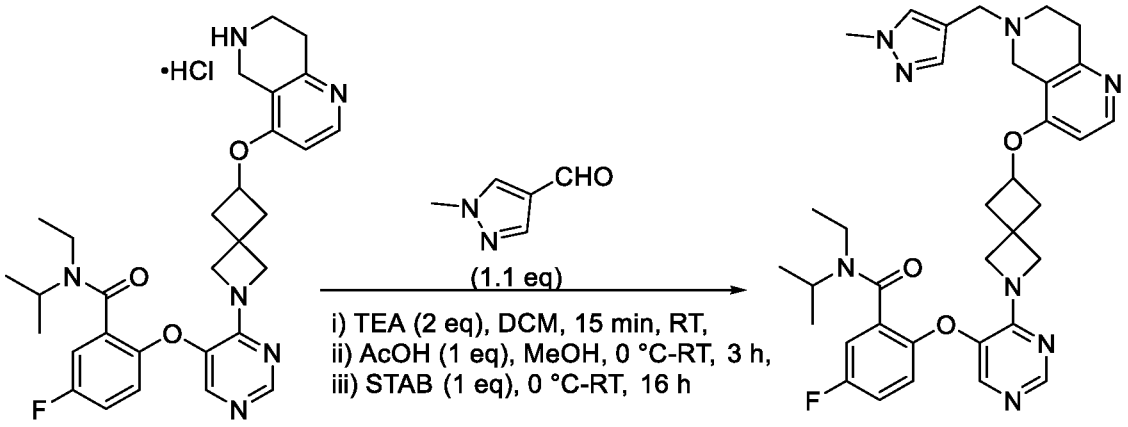
Example 225. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-5-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 96)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.1 equivalents of 1-methyl-1H-pyrazole-5-carbaldehyde was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-5-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 87%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.30 - 7.22 (m, 2H), 7.09 - 6.99 (m, 1H), 6.70 - 6.65 (m, 1H), 6.20 (d, J = 1.6 Hz, 1H), 4.73 (quin, J = 6.6 Hz, 1H), 4.46 - 4.06 (m, 4H), 3.79 (s, 3H), 3.78 - 3.76 (m, 1H), 3.73 (s, 2H), 3.50 (s, 2H), 3.43 - 3.38 (m, 1H), 3.25 - 3.14 (m, 1H), 2.83 - 2.68 (m, 6H), 2.28 - 2.20 (m, 2H), 1.25 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.72 min, m/z = 641.6 $[M+H]^+$; HPLC (Method A): Rt = 5.21 min, 95.02%.

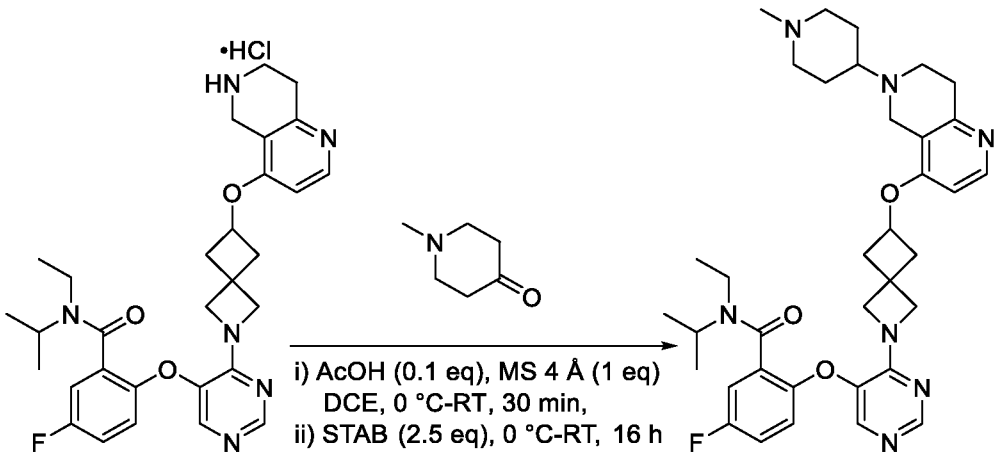
Example 226. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methyl-1H-pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 95)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.1 equivalents of 1-methyl-1H-pyrazole-4-carbaldehyde was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((4-(6-((6-((1H-pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 12.58%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.61 (s, 1H), 7.34 (s, 1H), 7.31 - 7.22 (m, 2H), 7.11 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.77 - 4.68 (m, 1H), 4.46 - 4.08 (m, 4H), 3.81 (s, 3H), 3.78 - 3.71 (m, 1H), 3.54 (s, 2H), 3.42 (s, 2H), 3.40 - 3.37 (m, 1H), 3.29 - 3.17 (m, 1H), 2.82 - 2.64 (m, 6H), 2.27 - 2.20 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.64 min, m/z = 641.4 $[M+H]^+$; HPLC (Method A): Rt = 5.05 min, 99.72%.

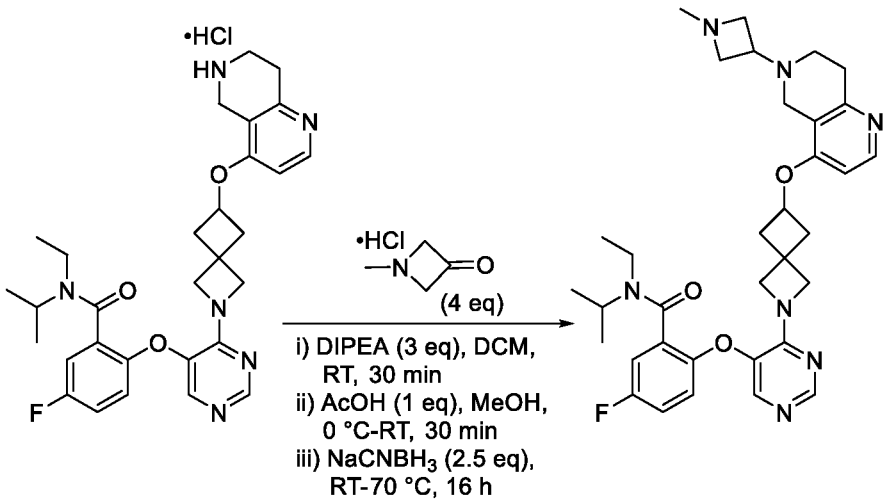
Example 227. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-methylpiperidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 76)



This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1 equivalent of 1-methylpiperidin-4-one, except that 0.1 equivalent of AcOH and 2.5 equivalents of STAB were used. The crude was purified by Prep HPLC (Method A) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-methylpiperidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 35.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.19 - 8.13 (m, 1H), 7.77 - 7.60 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 6.97 (m, 1H), 6.69 - 6.62 (m, 1H), 4.75-4.73 (m, 1H), 4.53 - 4.03 (m, 3H), 3.75-3.70 (m, 1H), 3.54 (bs, 2H), 3.40 - 3.03 (m, 3H), 2.85 - 2.65 (m, 8H), 2.41 - 2.32 (m, 1H), 2.31 - 2.21 (m, 2H), 2.15 (s, 3H), 1.92 - 1.82 (m, 2H), 1.82 - 1.72 (m, 2H), 1.58 - 1.43 (m, 2H), 1.19 - 0.94 (m, 9H); LCMS (Method D): Rt = 1.73 min, m/z = 644.3 $[M+H]^+$; HPLC (Method A): Rt = 4.93 min, 99.89%.

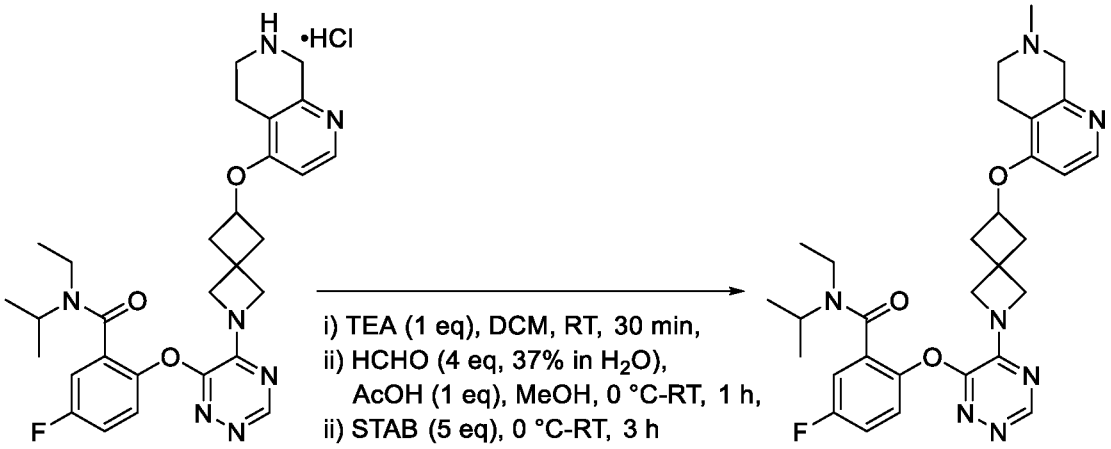
Example 228. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-methylazetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 133)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 4 equivalents of 1-methylazetidin-3-one hydrochloride, 3 equivalents of DIPEA and 2.5 equivalents of $NaCNBH_3$ were used. The reaction was stirred at 70 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-methylazetidin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 45.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.22 - 8.15 (m, 1H), 7.76 - 7.64 (m, 1H), 7.35 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.06 (m, 4H), 3.82 - 3.69 (m, 1H), 3.50 - 3.42 (m, 2H), 3.42 - 3.36 (m, 1H), 3.30 - 3.11 (m, 3H), 3.05 (p, J = 6.4 Hz, 1H), 2.85 - 2.72 (m, 6H), 2.59 - 2.53 (m, 2H), 2.30 - 2.25 (m, 2H), 2.22 (s, 3H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.63 min, m/z = 616.3 $[M+H]^+$; HPLC (Method A): Rt = 4.80 min, 97.08%.

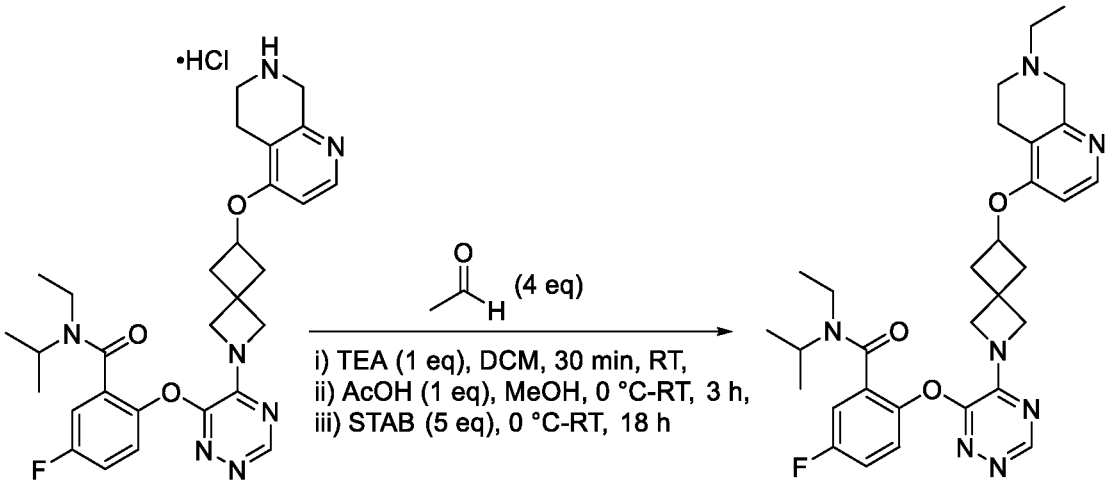
Example 229. *N*-ethyl-5-fluoro-N-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 195)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 4 equivalents of formaldehyde (37% in H_2O), except that 1 equivalent of TEA and 5 equivalents of STAB were used. The reaction was quenched with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 46.9%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.48 - 7.32 (m, 3H), 6.70 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.7 Hz, 1H), 4.67 - 4.46 (m, 2H), 4.32 - 4.11 (m, 2H), 3.67 - 3.58 (m, 1H), 3.48 (br s, 2H), 3.15 - 3.01 (m, 1H), 2.90 - 2.75 (m, 2H), 2.66 - 2.55 (m, 5H), 2.40 - 2.25 (m, 4H), 1.16 - 0.67 (m, 9H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.23 min, m/z = 662.0 $[M+H]^+$; HPLC (Method D): Rt = 2.54 min, 99.18%.

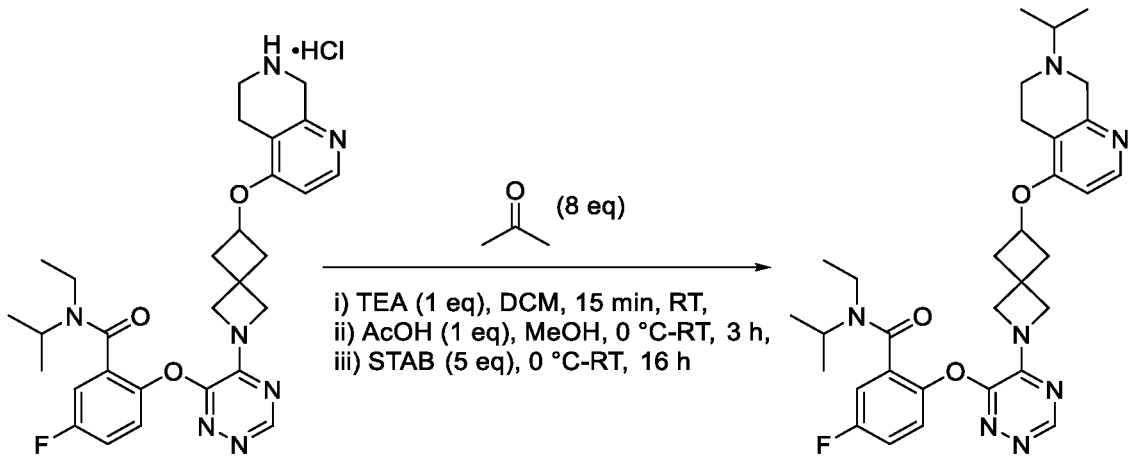
Example 230. *N*-Ethyl-2-((5-(6-((7-ethyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 200)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 4 equivalents of acetaldehyde, except that 1 equivalent of Et_3N and 5 equivalents of STAB were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product was impure. Therefore, it was re-purified by purified by Prep HPLC (Method AC). The fractions were concentrated under reduced pressure and lyophilized to obtain *N*-ethyl-2-((5-(6-((7-ethyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 2.95%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 6.69 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.68 - 4.48 (m, 2H), 4.34 - 4.08 (m, 2H), 3.68 - 3.56 (m, 1H), 3.49 (s, 2H), 3.43 - 3.36 (m, 1H), 3.15 - 2.99 (m, 2H), 2.83 (br s, 2H), 2.62 (br s, 4H), 2.38 - 2.27 (m, 2H), 1.15 - 0.66 (m, 12H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.78 min, m/z = 576.3 $[M+H]^+$; HPLC (Method A): Rt = 5.14 min, 97.38%.

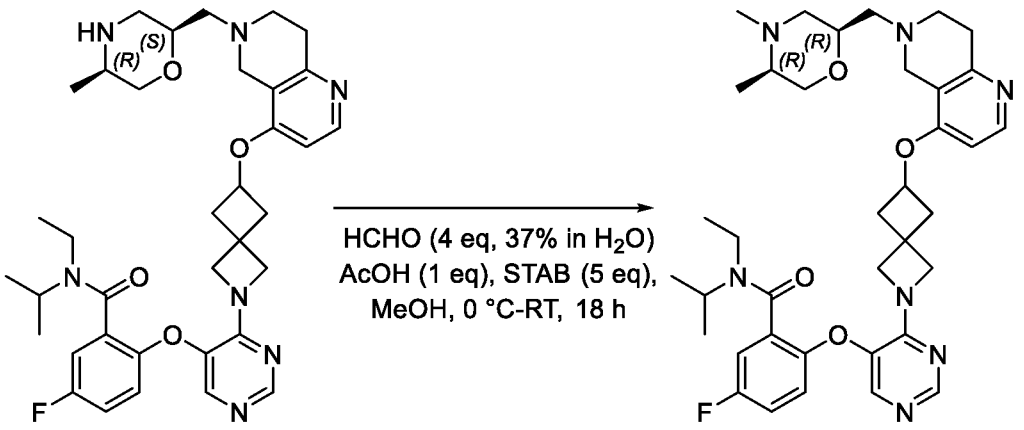
Example 231. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 227)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride and 8 equivalents of acetone, except that 1 equivalent of Et_3N and 5 equivalents of STAB were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method K). ^{1}HNMR of the product showed impurity peaks. Therefore, the impure product was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((7-isopropyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

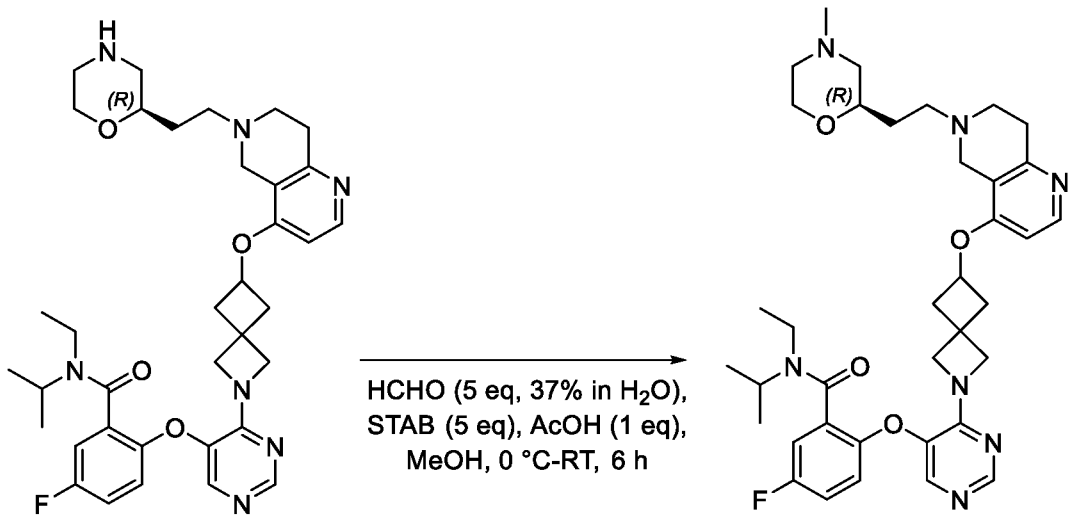
Yield: 15.02%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 - 8.15 (m, 1H), 7.48 - 7.32 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.67 - 4.47 (m, 2H), 4.33 - 4.11 (m, 2H), 3.67 - 3.60 (m, 1H), 3.58 (s, 2H), 3.47 - 3.36 (m, 1H), 3.17 - 2.99 (m, 1H), 2.91 - 2.77 (m, 3H), 2.70 - 2.64 (m, 2H), 2.61 - 2.56 (m, 2H), 2.37 - 2.26 (m, 2H), 1.17 - 0.69 (m, 15H); LCMS (Method D): Rt = 1.88 min, m/z = 590.3 $[M+H]^+$; HPLC (Method A): Rt = 5.32 min, 99.77%.

Example 232. 2-((4-(6-(((6-(((2*R*,5*R*)-4,5-Dimethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 294)



In a 25 mL round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2S,5R)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (140 mg, 0.212 mmol) was dissolved in MeOH (1 mL). To this solution, formaldehyde (0.069 mL, 0.849 mmol, 37 wt% in H_2O) and AcOH (12.74 mg, 0.212 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. STAB (225 mg, 1.061 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 18 h. The progress was monitored by TLC(15% MeOH in DCM). After completion, the reaction was quenched with aq. $NaHCO_3$ (10 mL) and extracted with 10% MeOH in DCM (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(((2*R*,5*R*)-4,5-dimethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (90 mg, 62.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.21 - 8.16 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.80 - 4.70 (m, 1H), 4.31 - 4.07 (m, 4H), 3.81 - 3.68 (m, 2H), 3.58 - 3.37 (m, 4H), 3.29 - 3.12 (m, 2H), 2.85 - 2.74 (m, 5H), 2.73 - 2.64 (m, 1H), 2.63 - 2.56 (m, 1H), 2.48 - 2.42 (m, 2H), 2.41 - 2.32 (m, 2H), 2.30 - 2.21 (m, 2H), 2.17 (s, 3H), 1.25 - 0.97 (m, 9H), 0.93 (d, J = 6.5 Hz, 3H); LCMS (Method G): Rt = 1.84 min, m/z = 674.7 $[M+H]^+$; HPLC (Method A): Rt = 5.14 min, 99.60%; Chiral SFC (Method B): Rt = 1.32 min, 99.76%.

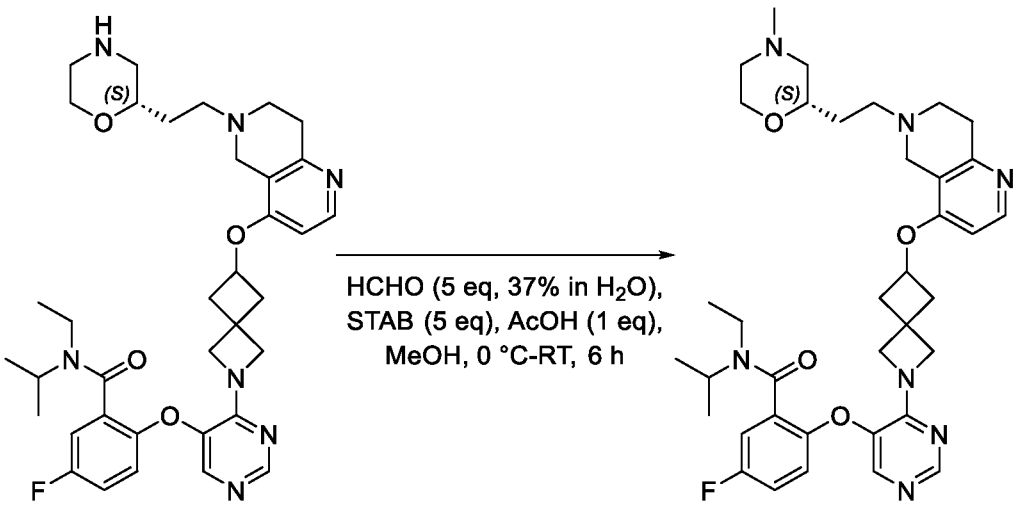
Example 233. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 297)



This compound was synthesized following the procedure described for the synthesis of Example 232, starting with 1 equivalent of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 5 equivalents of formaldehyde (37 wt% in H_2O) was used. After completion, the reaction was diluted with EtOAc and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was Prep HPLC (Method I) to afford (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (38.43 mg, 37.5% yield) as a solid.

Yield: 37.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.79 - 7.65 (m, 1H), 7.35 - 7.20 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.63 (m, 1H), 4.80 - 4.70 (m, 1H), 4.33 - 4.06 (m, 4H), 3.81 - 3.70 (m, 2H), 3.51 - 3.36 (m, 5H), 3.27 - 3.09 (m, 1H), 2.86 - 2.74 (m, 4H), 2.74 - 2.62 (m, 3H), 2.60 - 2.55 (m, 3H), 2.32 - 2.22 (m, 2H), 2.15 (s, 3H), 1.93 (dt, J = 3.2, 11.3 Hz, 1H), 1.74 - 1.55 (m, 3H), 1.30 - 0.88 (m, 9H); LCMS (Method G): Rt = 1.72 min, m/z = 674.4 $[M+H]^+$; HPLC (Method A): Rt = 4.94 min, 99.57%; Chiral SFC (Method AJ): Rt = 3.28 min, 98.82%.

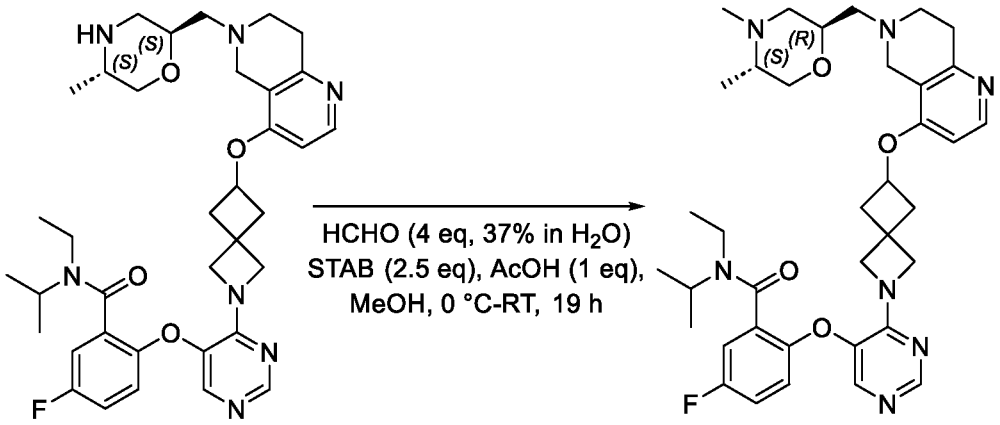
Example 234. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 298)



This compound was synthesized following the procedure described for the synthesis of Example 232, starting with 1 equivalent of (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 5 equivalents of formaldehyde (37% in H_2O) was used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method I) to afford (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 21.52%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.36 - 7.21 (m, 2H), 7.12 - 7.00 (m, 1H), 6.71 - 6.61 (m, 1H), 4.83 - 4.70 (m, 1H), 4.34 - 4.08 (m, 4H), 3.84 - 3.71 (m, 2H), 3.50 - 3.37 (m, 5H), 3.28 - 3.12 (m, 1H), 2.84 - 2.73 (m, 4H), 2.74 - 2.61 (m, 4H), 2.60 - 2.55 (m, 2H), 2.32 - 2.24 (m, 2H), 2.15 (s, 3H), 1.99 - 1.89 (m, 1H), 1.73 - 1.56 (m, 3H), 1.26 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.73 min, m/z = 674.7 $[M+H]^+$; HPLC (Method A): Rt = 4.94 min, 99.93%; Chiral SFC (Method AJ): Rt = 3.36 min, 96.77%.

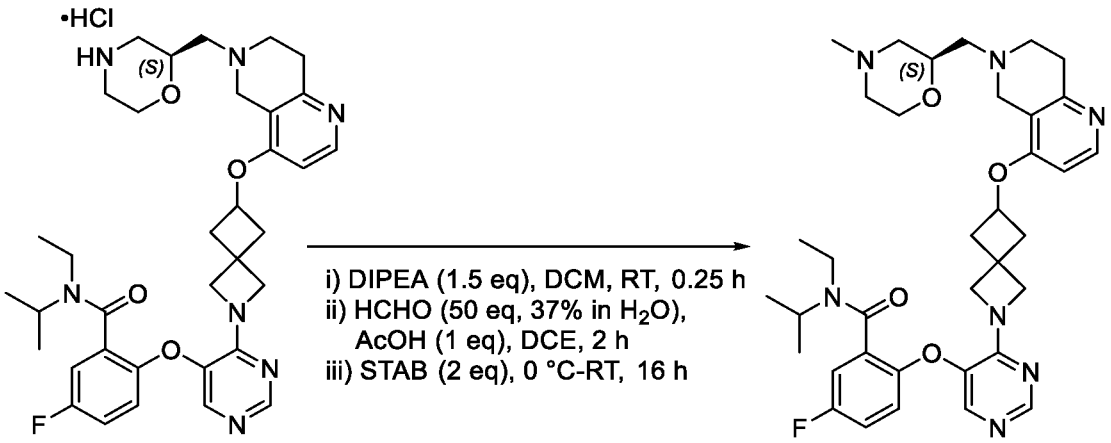
Example 235. 2-((4-(6-((6-(((2*R*,5*S*)-4,5-Dimethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 302)



This compound was synthesized following the procedure described for the synthesis of Example 232, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(((2*S*,5*S*)-5-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and 4 equivalents of formaldehyde (37% in H_2O), except that 2.5 equivalents of STAB was used. After completion, the crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(((2*R*,5*S*)-4,5-dimethylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

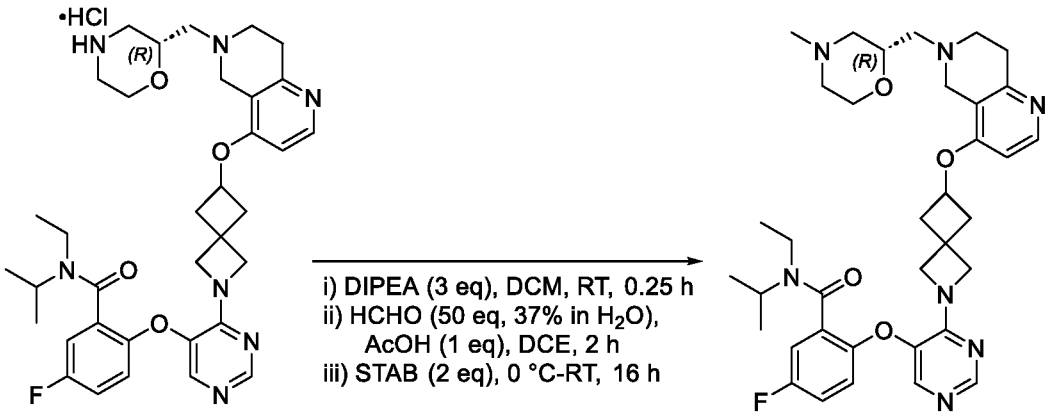
Yield:58.10%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.64 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.82 - 4.68 (m, 1H), 4.33 - 4.06 (m, 5H), 3.82 - 3.60 (m, 3H), 3.47 (s, 2H), 3.44 - 3.35 (m, 1H), 3.29 - 3.13 (m, 2H), 3.09 (t, *J* = 10.8 Hz, 1H), 2.84 - 2.73 (m, 6H), 2.71 - 2.65 (m, 1H), 2.31 - 2.20 (m, 2H), 2.15 (s, 3H), 1.99 - 1.88 (m, 1H), 1.83 (dd, *J* = 10.5, 11.5 Hz, 1H), 1.27 - 0.97 (m, 9H), 0.88 (d, *J* = 6.0 Hz, 3H), one proton is merging with moisture peak; LCMS (Method G): Rt = 1.79 min, m/z = 674.6 $[M+H]^+$; HPLC (Method A): Rt = 5.18 min, 99.74%. Chiral SFC (Method J): Rt = 3.40 min, 95.89%.

Example 236. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 222)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 1.5 equivalents of DIPEA and 2 equivalents of STAB were used, and DCE was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 53.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.47 - 4.08 (m, 4H), 3.80 - 3.71 (m, 2H), 3.68 - 3.60 (m, 1H), 3.54 - 3.49 (m, 1H), 3.47 (br s, 2H), 3.44 - 3.37 (m, 1H), 3.29 - 3.12 (m, 2H), 2.84 - 2.74 (m, 6H), 2.73 - 2.66 (m, 2H), 2.61 - 2.57 (m, 1H), 2.31 - 2.21 (m, 2H), 2.16 (s, 3H), 1.98 - 1.90 (m, 1H), 1.70 (t, J = 10.6 Hz, 1H), 1.15 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.78 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.90 min, 97.24%; Chiral SFC (Method J): Rt = 3.98 min, 97.16%.

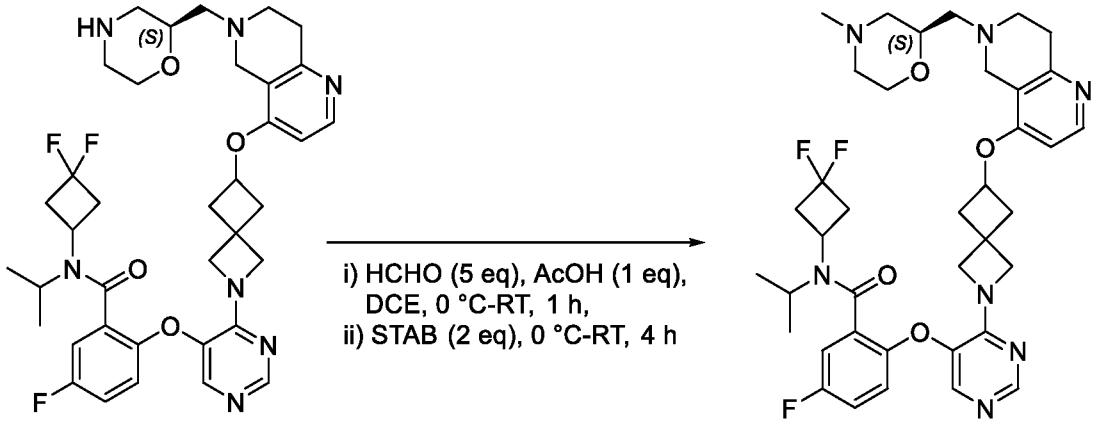
Example 237. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 223)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 2 equivalents of STAB and 3 equivalents of DIPEA were used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 68.3%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 - 8.40 (m, 1H), 8.24 (d, *J* = 5.7 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.09 - 7.00 (m, 2H), 6.78 - 6.69 (m, 1H), 6.38 (d, *J* = 5.7 Hz, 1H), 4.70 - 4.60 (m, 1H), 4.41 - 4.15 (m, 4H), 3.98 - 3.83 (m, 3H), 3.74 (t, *J* = 11.0 Hz, 1H), 3.67 - 3.55 (m, 2H), 3.55 - 3.47 (m, 1H), 3.43 - 3.33 (m, 1H), 3.27 - 3.19 (m, 1H), 3.05 - 2.98 (m, 2H), 2.93 - 2.67 (m, 6H), 2.58 - 2.50 (m, 1H), 2.43 - 2.35 (m, 2H), 2.34 (s, 3H), 2.21 - 2.15 (m, 1H), 1.90 (br t, *J* = 10.5 Hz, 1H), 1.34 - 1.26 (m, 4H), 1.20 - 1.09 (m, 5H); LCMS (Method D): Rt = 1.77 min, m/z = 660.4 $[M+H]^+$; HPLC (Method A): Rt = 4.91 min, 99.45%; Chiral SFC (Method J): Rt = 3.90 min, 98.73%.

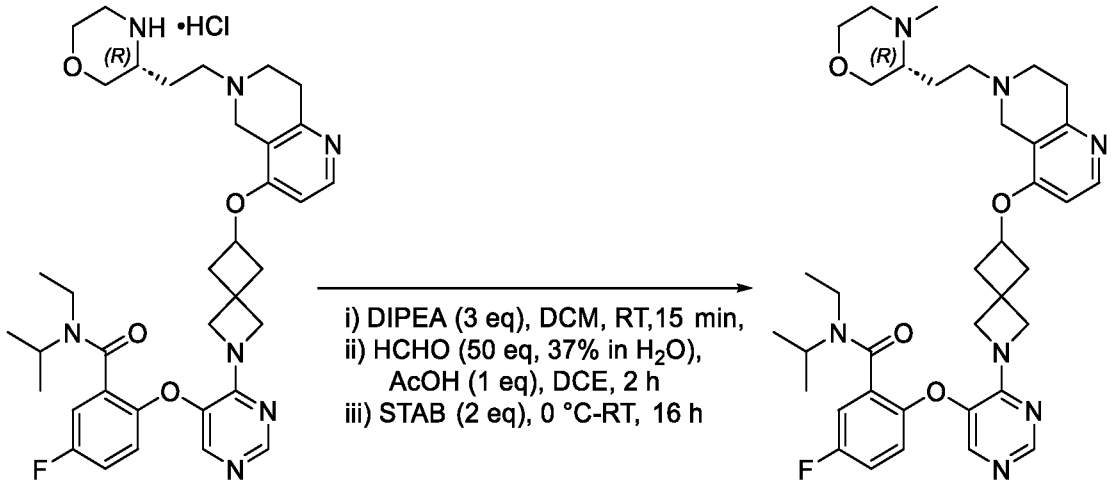
Example 238. (*S*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 247)



This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of (*S*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(morpholin-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and 5 equivalents of formaldehyde (neat), except that 2 equivalents of STAB was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((4-methylmorpholin-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 48.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (d, *J* = 5.5 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, *J* = 3.0, 8.2 Hz, 1H), 7.27 (dt, *J* = 2.9, 8.7 Hz, 1H), 7.06 (dd, *J* = 4.3, 9.0 Hz, 1H), 6.65 (d, *J* = 5.7 Hz, 1H), 4.74 (quin, *J* = 6.6 Hz, 1H), 4.32 - 4.07 (m, 4H), 3.97 - 3.85 (m, 1H), 3.79 - 3.60 (m, 5H), 3.54 - 3.49 (m, 1H), 3.47 (s, 2H), 2.83 - 2.69 (m, 9H), 2.60 - 2.54 (m, 3H), 2.30 - 2.22 (m, 2H), 2.16 (s, 3H), 1.94 (dt, *J* = 3.2, 11.4 Hz, 1H), 1.70 (t, *J* = 10.7 Hz, 1H), 1.48 - 0.98 (m, 6H); LCMS (Method G): Rt = 1.97 min, m/z = 722.4 $[M+H]^+$; HPLC (Method A): Rt = 5.52 min, 99.11%; Chiral SFC (Method AC): Rt = 1.13 min, 98.97%.

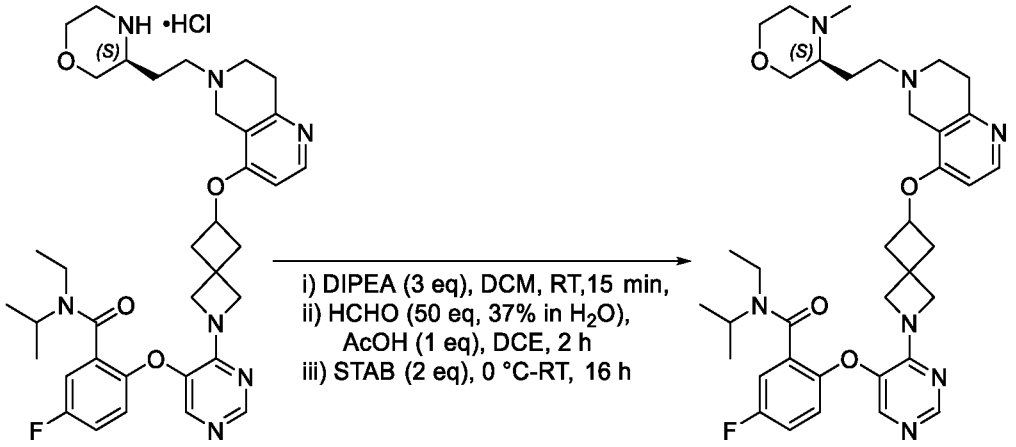
Example 239. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 274)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 3 equivalents of DIPEA and 2 equivalents of STAB were used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

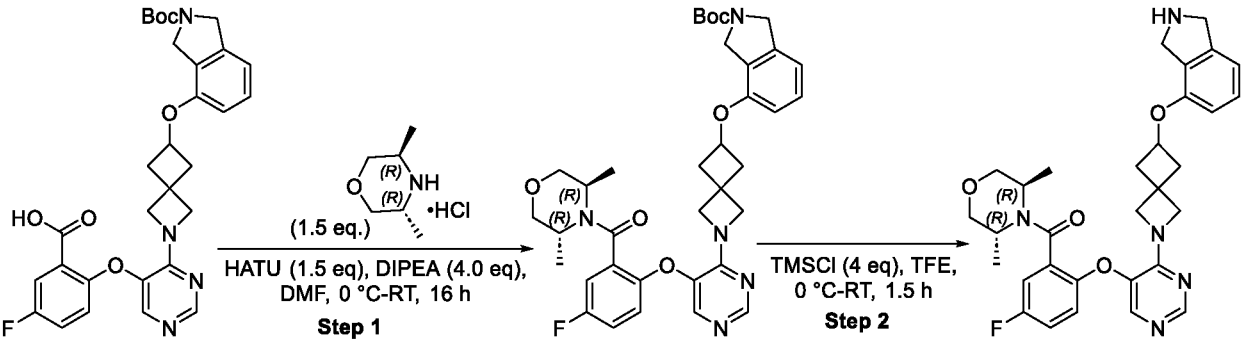
Yield: 21.46%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 - 8.15 (m, 1H), 7.79 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 6.99 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.70 (m, 1H), 4.47 - 4.07 (m, 4H), 3.80 - 3.72 (m, 1H), 3.71 - 3.62 (m, 2H), 3.49 - 3.39 (m, 4H), 3.27 - 3.16 (m, 2H), 2.84 - 2.74 (m, 4H), 2.71 - 2.59 (m, 4H), 2.30 - 2.22 (m, 2H), 2.19 (s, 3H), 2.18 - 2.01 (m, 3H), 1.80 - 1.70 (m, 1H), 1.52 - 1.41 (m, 1H), 1.14 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.72 min, m/z = 674.7 $[M+H]^+$; HPLC (Method A): Rt = 4.87 min, 99.41%; Chiral SFC (Method AJ): Rt = 3.87 min, 98.63%.

Example 240. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 303)

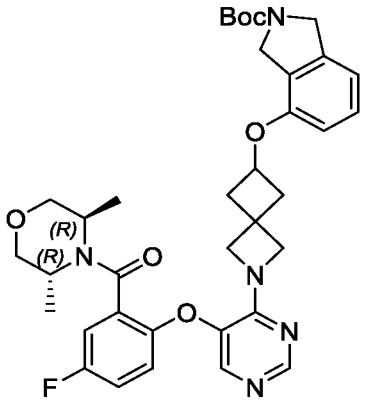


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(morpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 3 equivalents of DIPEA and 2 equivalents of STAB were used. The crude product was purified by Prep HPLC (Method B) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(4-methylmorpholin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 27.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.16 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.49 - 4.05 (m, 4H), 3.82 - 3.71 (m, 1H), 3.71 - 3.62 (m, 2H), 3.49 - 3.37 (m, 4H), 3.27 - 3.11 (m, 2H), 2.84 - 2.73 (m, 4H), 2.72 - 2.61 (m, 4H), 2.30 - 2.22 (m, 2H), 2.19 (s, 3H), 2.18 - 2.01 (m, 3H), 1.81 - 1.70 (m, 1H), 1.52 - 1.41 (m, 1H), 1.15 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.79 min, m/z = 674.4 $[M+H]^+$; HPLC (Method A): Rt = 4.88 min, 96.79%; Chiral SFC (Method K): Rt = 6.71 min, 96.18%.

Example 241. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 5)



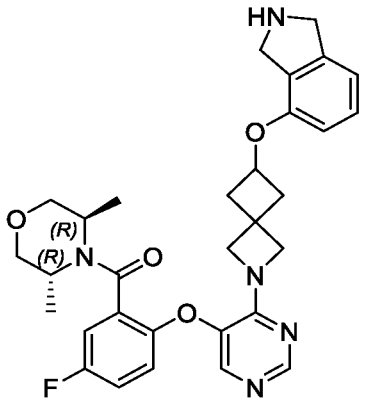
Step 1. tert-Butyl 4-((2-(5-(2-((3R,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 2-((4-(6-((2-(*tert*-butoxycarbonyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid and 1.5 equivalents of (3*R*,5*R*)-3,5-dimethylmorpholine hydrochloride, except that 4 equivalents of DIPEA was used. The reaction was quenched with cold water under vigorous stirring. The solid was filtered, washed with water, and dried under vacuum to obtain crude *tert*-butyl 4-((2-(5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 83%; LCMS (Method D): Rt = 2.26 min, m/z = 660.2 $[M+H]^+$, 97.68%. This material was used without further purification.

Step 2. ((3R,5R)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone

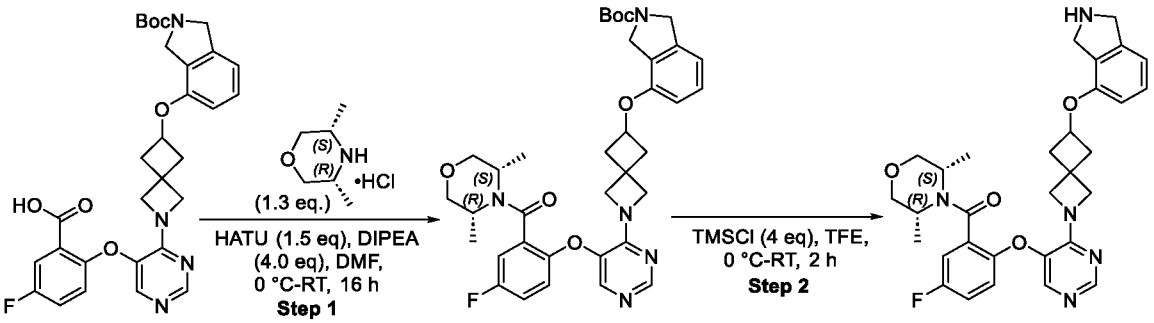


This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl 4-((2-(5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 4 equivalents of TMSCl was used, and TFE was used as a solvent. After completion, the reaction was concentrated under reduced pressure to afford crude (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-

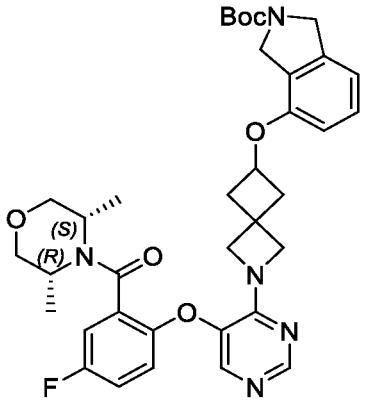
azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone hydrochloride. The crude was purified by Prep HPLC (Method D) to obtain the pure compound (3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone as a solid.

Yield: 55.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 7.70 (s, 1H), 7.41 - 7.34 (m, 1H), 7.33 - 7.26 (m, 1H), 7.14 - 7.02 (m, 2H), 6.90 - 6.80 (m, 1H), 6.73 - 6.59 (m, 1H), 4.72 - 4.62 (m, 1H), 4.28 - 4.12 (m, 4H), 4.03 (br s, 2H), 3.97 (br s, 2H), 3.94 - 3.60 (m, 4H), 3.58 - 3.41 (m, 2H), 2.81 - 2.71 (m, 2H), 2.30 - 2.18 (m, 2H), 1.19 (s, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.34 min, m/z = 560.1[M+H]$^+$; HPLC (Method A): Rt = 4.71 min, 99.80%; Chiral SFC (Method K): Rt = 5.67 min, 100%.

Example 242. ((3*S*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 8)



Step 1. tert-Butyl 4-((2-(5-(2-((3S,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate

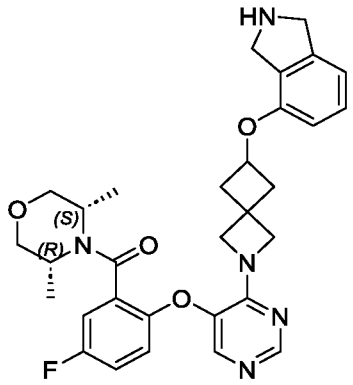


This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 2-((4-(6-((2-(*tert*-butoxycarbonyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid and 1.3 equivalents of (3*S*,5*R*)-3,5-dimethylmorpholine hydrochloride, except that 4 equivalents of DIPEA was used. The reaction was quenched with cold water under vigorous stirring. The solid was filtered, washed with water, and dried under vacuum to obtain crude *tert*-butyl 4-

((2-(5-(2-((3*S*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 70.5%; LCMS (Method D): Rt = 2.22 min, m/z = 660.2 $[M+H]^+$, 71.86%. This material was used without further purification.

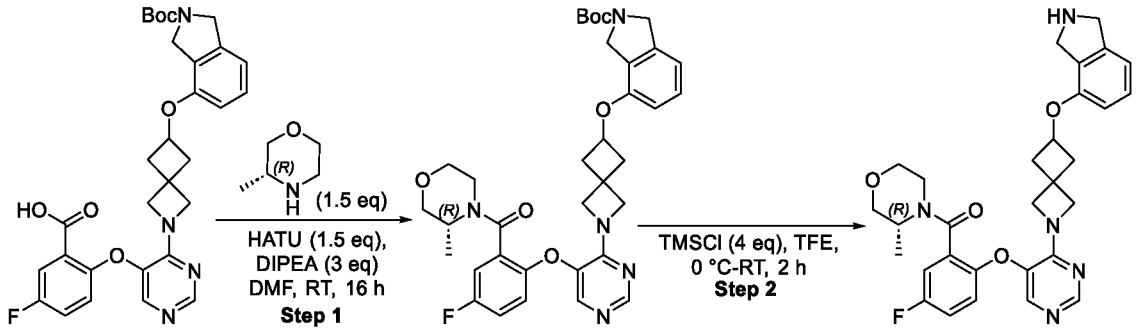
Step 2. ((3S,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone



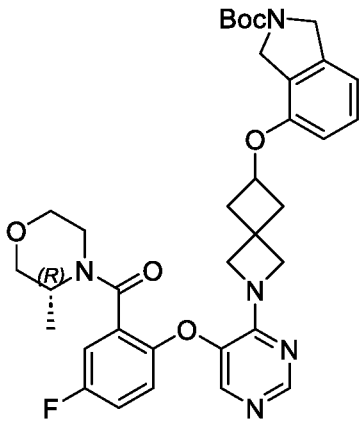
This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl 4-((2-(5-(2-((*3S,5R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 4 equivalents of TMSCl was used, and TFE was used as a solvent. After completion, the reaction was concentrated under reduced pressure to afford crude (3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone hydrochloride. The crude was purified by Prep HPLC (Method V) to obtain (3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone as a solid.

Yield: 27.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (m, 1H), 7.83 - 7.69 (m, 1H), 7.44 - 7.32 (m, 1H), 7.31 - 7.23 (m, 1H), 7.15 - 6.99 (m, 2H), 6.91 - 6.80 (m, 1H), 6.74 - 6.59 (m, 1H), 4.70 - 4.61 (m, 1H), 4.29 - 4.08 (m, 4H), 4.04 (br s, 2H), 3.98 (br s, 2H), 3.93 - 3.53 (m, 4H), 3.52 - 3.39 (m, 2H), 2.80 - 2.71 (m, 2H), 2.29 - 2.18 (m, 2H), 1.39 - 1.16 (m, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.63 min, m/z = 560.3 $[M+H]^+$; HPLC (Method A): Rt = 4.74 min, 98.72%; Chiral SFC (Method E): Rt 1.95 min, 100%.

Example 243. (*R*)-(5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)(3-methylmorpholino)methanone (Compound No. 9)



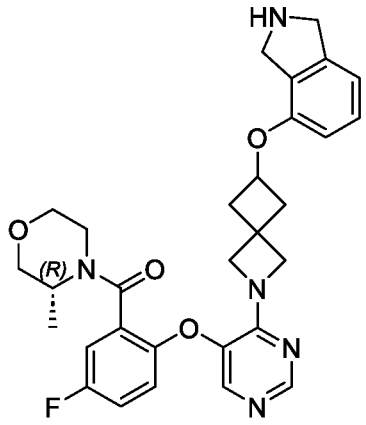
Step 1. tert-Butyl (R)-4-((2-(5-(4-fluoro-2-(3-methylmorpholine-4-carbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 2-((4-(6-((2-(*t*ert-butoxycarbonyl) isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid and 1.5 equivalents of (*R*)-3-methylmorpholine. The reaction was quenched with cold water under vigorous stirring. The solid was filtered, washed with water, and dried under vacuum to obtain crude *ter*t-butyl (*R*)-4-((2-(5-(4-fluoro-2-(3-methylmorpholine-4-carbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate as a solid.

Yield: 83%; LCMS (Method D): Rt = 2.16 min, m/z = 646.2 $[M+H]^+$, 95.51%. This material was used without further purification.

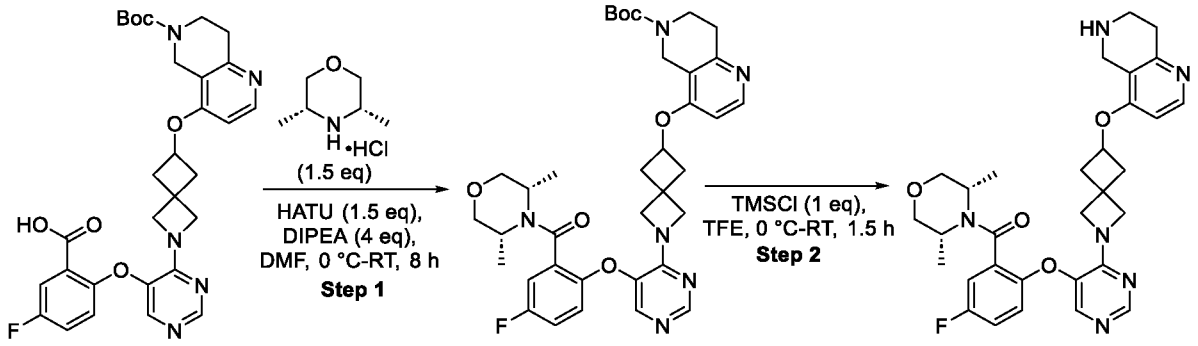
Step 2. (R)-(5-Fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)(3-methylmorpholino)methanone



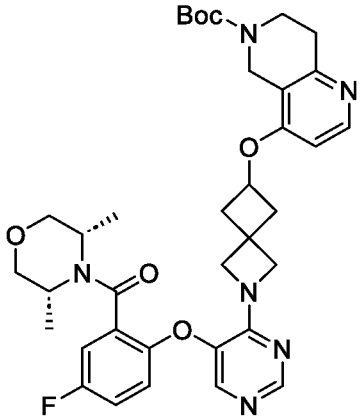
This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl (*R*)-4-((2-(5-(4-fluoro-2-(3-methylmorpholine-4-carbonyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-2-carboxylate, except that 4 equivalents of TMSCl was used, and TFE was used as a solvent. After completion, the reaction was concentrated under reduced pressure to obtain crude (*R*)-(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)(3-methylmorpholino)methanone hydrochloride. The crude was purified by Prep HPLC (Method S) to obtain (*R*)-(5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)(3-methylmorpholino)methanone as a solid.

Yield: 49.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 - 8.27 (m, 1H), 7.83 - 7.70 (m, 1H), 7.39 - 7.23 (m, 2H), 7.11 (t, J = 7.7 Hz, 1H), 7.07 - 6.99 (m, 1H), 6.91 - 6.80 (m, 1H), 6.74 - 6.59 (m, 1H), 4.75 - 4.55 (m, 1H), 4.52 - 4.42 (m, 1H), 4.34 - 4.07 (m, 4H), 4.04 (br s, 2H), 3.98 (br s, 2H), 3.93 - 3.83 (m, 1H), 3.75 - 3.50 (m, 2H), 3.28 - 2.96 (m, 3H), 2.81 - 2.70 (m, 2H), 2.28 - 2.18 (m, 2H), 1.33 - 1.05 (m, 3H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.50 min, m/z = 546.3 $[M+H]^+$; HPLC (Method A): Rt = 4.51 min, 99.26%; Chiral SFC (Method C): Rt = 3.47 min, 100%.

Example 244. ((3*R*,5*S*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 55)



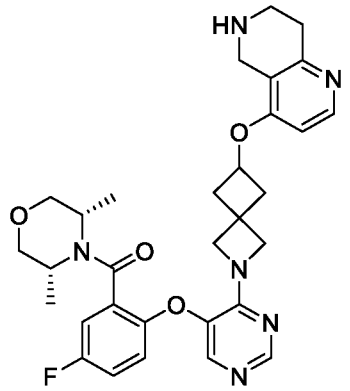
Step 1. tert-Butyl 4-((2-(5-(2-((3R,5S)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid, except that 1.5 equivalents of (3*R*,5*S*)-3,5-dimethylmorpholine hydrochloride and 4 equivalents of DIPEA were used. The reaction was poured into ice-cold water and stirred for 5 min. The resulting solid was filtered, and the solid was under reduced pressure to obtain crude *tert*-butyl 4-((2-(5-(2-((3*R*,5*S*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

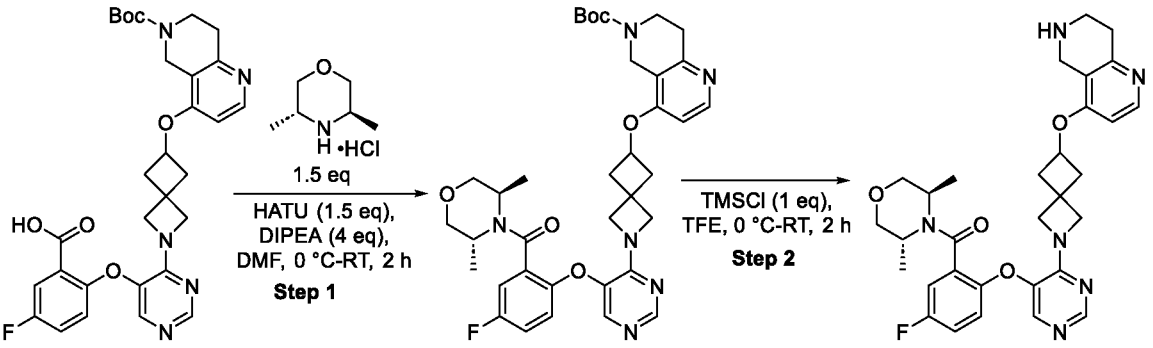
Yield: 70.4%; LCMS (Method D): Rt = 1.28 min, m/z = 675.2$[M+H]^+$, 91.42%.

Step 2. ((3R,5S)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone

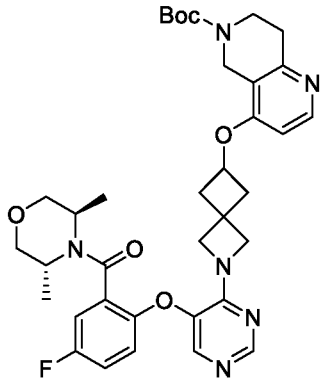


This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl 4-((2-(5-(2-((3*R*,5*S*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1 equivalent of TMSCl and TFE was used as a solvent. After completion, the reaction was concentrated under reduced pressure to obtain ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone. Yield: 52.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.83 - 7.71 (m, 1H), 7.47 - 7.23 (m, 2H), 7.15 - 6.96 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.72 (quin, J = 6.5 Hz, 1H), 4.47 - 4.06 (m, 5H), 3.79 - 3.54 (m, 5H), 3.26 - 3.09 (m, 1H), 2.95 (t, J = 5.8 Hz, 2H), 2.83 - 2.74 (m, 2H), 2.67 (t, J = 5.0 Hz, 2H), 2.30 - 2.18 (m, 2H), 1.45 - 0.97 (m, 6H) two protons merged with solvent peaks; LCMS (Method D): Rt = 1.55 min, m/z = 575.3 $[M+H]^+$; HPLC (Method A): Rt = 4.41 min, 99.06%; Chiral SFC (Method AB) Rt = 1.59 min, 100%.

Example 245. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 56)



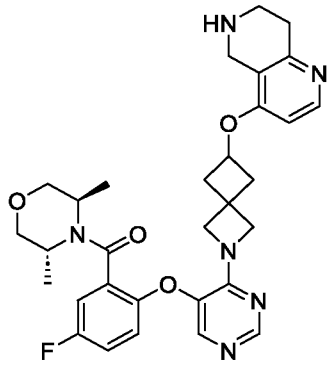
Step 1. tert-Butyl 4-((2-(5-(2-((3R,5R)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 2-((4-(6-((6-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid, except that 1.5 equivalents of (3*R*,5*R*)-3,5-dimethylmorpholine hydrochloride and 4 equivalents DIPEA were used. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 50% EtOAc in hexane) to afford *tert*-butyl 4-((2-(5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

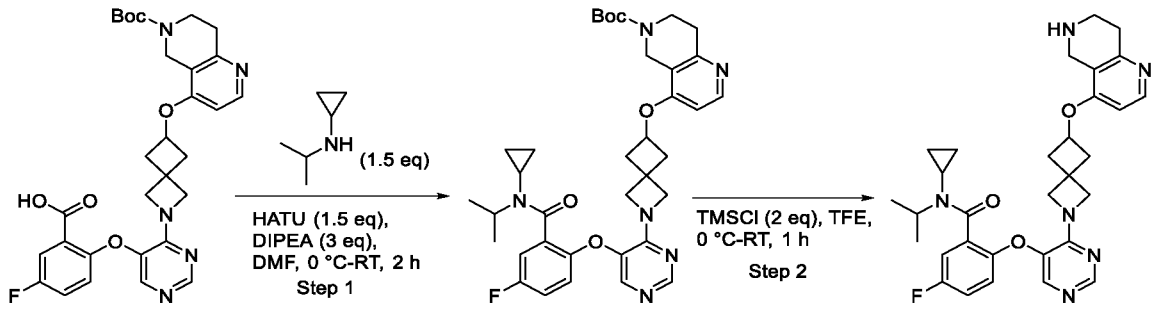
Yield: 86%; LCMS (Method B): Rt = 1.83 min, m/z = 675.2 $[M+H]^+$, 97.62%.

Step 2. ((3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone

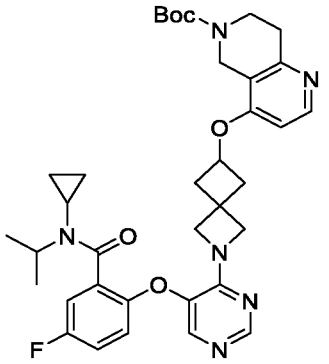


This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, Starting with *tert*-butyl 4-((2-(5-(2-((3*R*,5*R*)-3,5-dimethylmorpholine-4-carbonyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 1 equivalent of TMSCl, and TFE was used as a solvent. After completion, the reaction was concentrated under reduced pressure to obtain crude ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone hydrochloride. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone. Yield: 49.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.16 (d, J = 5.7 Hz, 1H), 7.70 (s, 1H), 7.43 - 7.34 (m, 1H), 7.30 (dt, J = 3.1, 8.6 Hz, 1H), 7.05 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.7 Hz, 1H), 4.73 (quin, J = 6.5 Hz, 1H), 4.31 - 4.11 (m, 4H), 4.03 - 3.45 (m, 8H), 2.95 (t, J = 5.8 Hz, 2H), 2.83 - 2.74 (m, 2H), 2.68 (t, J = 5.5 Hz, 2H), 2.29 - 2.18 (m, 2H), 1.47 - 0.97 (m, 6H) one proton merged with solvent peaks; LCMS (Method D): Rt = 1.54 min, m/z = 575.3 $[M+H]^+$; HPLC (Method A): Rt = 4.40 min, 99.91%; Chiral SFC (Method AB) Rt = 1.70 min, 100%.

Example 246. *N*-Cyclopropyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 53)



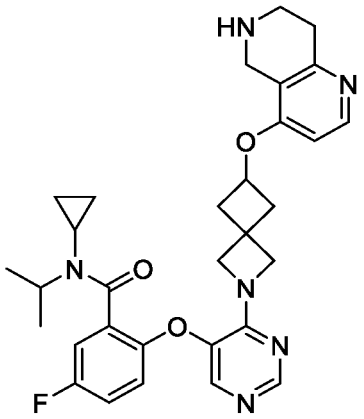
Step 1. tert-Butyl 4-((2-(5-(2-(cyclopropyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid, except that 1.5 equivalents of *N*-isopropylcyclopropanamine was used. The reaction was concentrated under reduced pressure. Ice water was added to the crude and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-(cyclopropyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 45.6%; LCMS (Method D): Rt = 2.27 min, m/z = 659.0 $[M+H]^+$; 52.38%.

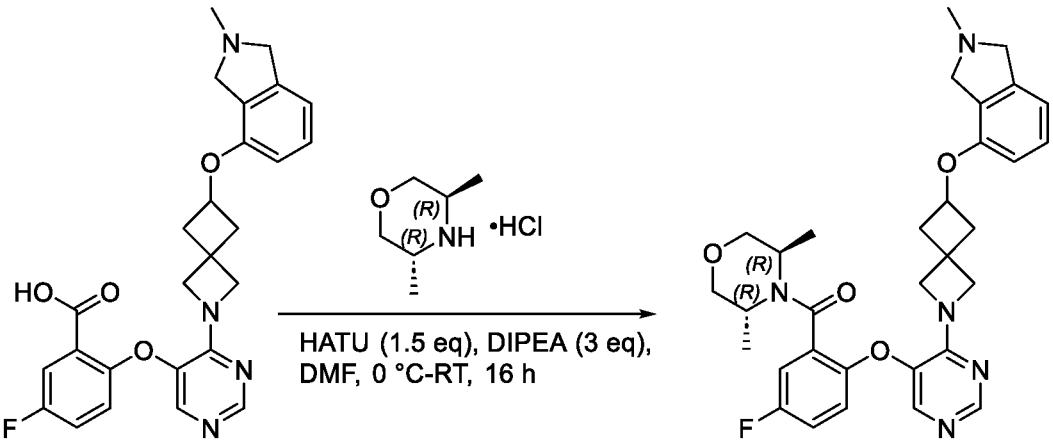
Step 2. N-Cyclopropyl-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl 4-((2-(5-(2-(cyclopropyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-

naphthyridine-6(5H)-carboxylate, except that 2 equivalents of TMSCl, and 2,2,2-trifluoroethanol was used as a solvent. The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-cyclopropyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 26.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.16 (d, *J* = 5.6 Hz, 1H), 7.71 (s, 1H), 7.36 - 7.28 (m, 1H), 7.24 (dt, *J* = 2.9, 8.5 Hz, 1H), 7.01 (dd, *J* = 4.4, 9.0 Hz, 1H), 6.65 (d, *J* = 5.6 Hz, 1H), 4.73 (quin, *J* = 6.4 Hz, 1H), 4.38 - 4.10 (m, 5H), 3.70 (s, 2H), 3.00 - 2.96 (m, 2H), 2.82 - 2.74 (m, 3H), 2.71 - 2.66 (m, 3H), 2.29 - 2.19 (m, 2H), 1.28 (br d, *J* = 6.3 Hz, 6H), 0.61 - 0.45 (m, 4H); LCMS (Method D): Rt = 1.78 min, m/z = 559.5 $[M+H]^+$; HPLC (Method A): Rt = 4.99 min, 96.90%.

Example 247. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 25)

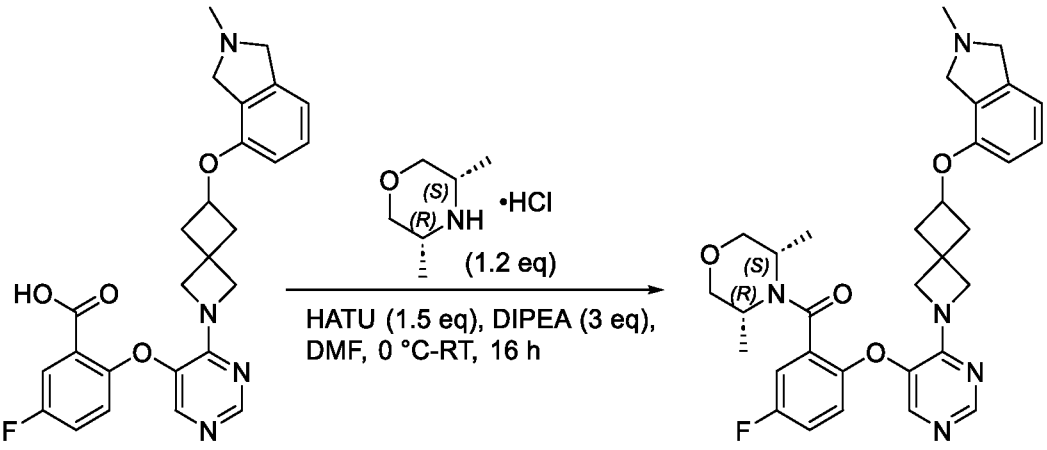


The reaction was performed following the same procedure in two batches (100 mg and 250 mg).

To a stirred solution of (3*R*,5*R*)-3,5-dimethylmorpholine hydrochloride (31.8 mg, 0.210 mmol) in DMF (5 mL) under a nitrogen atmosphere, DIPEA (81 mg, 0.630 mmol), HATU (120 mg, 0.315 mmol) and 5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid (100 mg, 0.210 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced

pressure. The crude product from both batches was combined and purified by Prep HPLC (Method U) to obtain ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (50.68 mg, 12.03% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.70 (s, 1H), 7.41 - 7.35 (m, 1H), 7.30 (dt, *J* = 3.2, 8.6 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 4.5, 9.1 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 4.66 (quin, *J* = 6.6 Hz, 1H), 4.26 - 4.13 (m, 4H), 3.95 - 3.82 (m, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.58 - 2.42 (m, 1H), 2.79 - 2.71 (m, 2H), 2.45 (s, 3H), 2.27 - 2.18 (m, 2H), 1.27 - 1.13 (m, 6H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.87 min, m/z = 574.3 $[M+H]^+$; HPLC (Method A): Rt = 5.72 min, 98.56%; Chiral SFC (Method N): Rt = 1.79 min, 100%.

Example 248. ((3*S*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone (Compound No. 26)

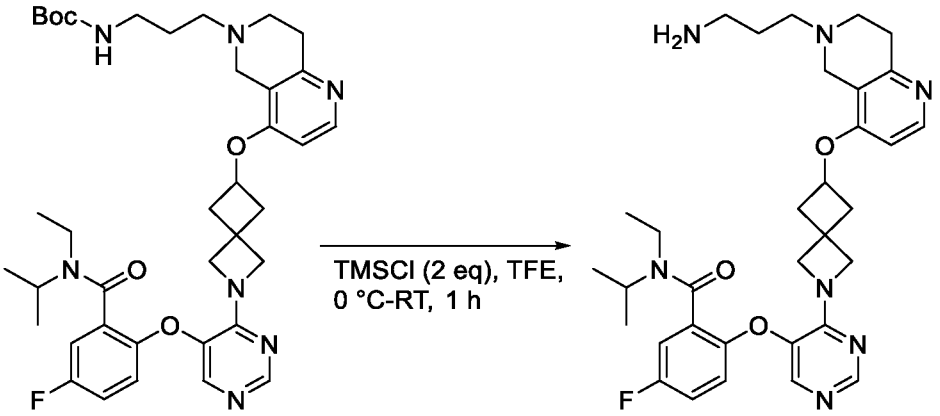


This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid and 1.2 equivalents of (3*S*,5*R*)-3,5-dimethylmorpholine hydrochloride. The crude product was purified by Prep HPLC (Method V) to obtain ((3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((4-(6-((2-methylisoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)phenyl)methanone as a solid.

Yield: 16.92%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 7.82 - 7.72 (m, 1H), 7.45 - 7.33 (m, 1H), 7.27 (dt, *J* = 2.8, 8.5 Hz, 1H), 7.14 - 7.09 (m, 1H), 7.07 - 6.99 (m, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 4.71 - 4.57 (m, 1H), 4.41 - 4.07 (m, 5H), 3.80 - 3.72 (m, 5H), 3.69 - 3.54 (m, 3H), 2.79 - 2.71 (m, 2H), 2.45 (s, 3H), 2.28 - 2.20 (m, 2H), 1.38

- 1.19 (m, 6H), one proton merged with solvent peak: LCMS (Method D): Rt = 1.08 min, m/z = 574.6 $[M+H]^+$; HPLC (Method A): Rt = 5.90 min, 99.90 %; Chiral SFC (Method O): Rt = 4.62 min, 97.77%.

Example 249. 2-((4-(6-((6-(3-Aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 128)

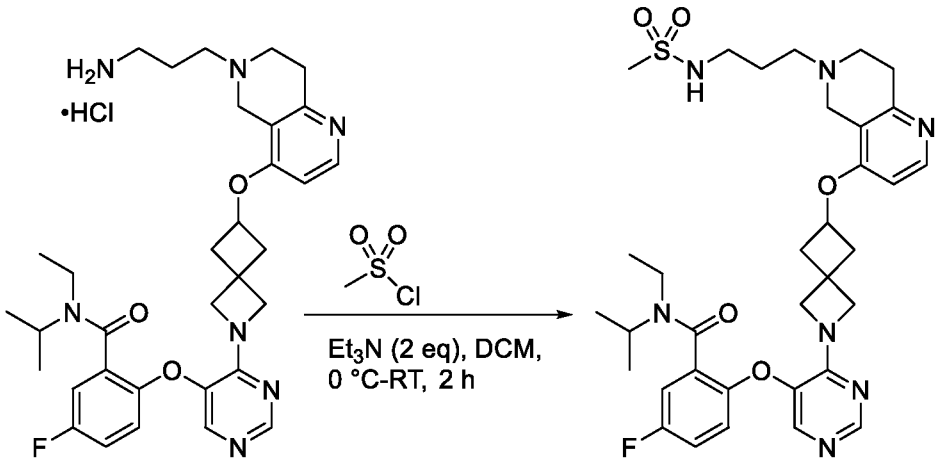


In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate (0.39 g, 0.554 mmol) was added in 2,2,2-trifluoroethanol (5 mL). TMSCl (0.150 mL, 1.108 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was triturated with EtOAc and filtered, and the solid was dried under vacuum to obtain 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.33 g, 93% yield) as a solid. LCMS (Method C): Rt = 1.61 min, m/z = 604.4 $[M+H]^+$; 98.32%.

30 mg of this compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (15 mg) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.67 (m, 1H), 7.30 - 7.21 (m, 2H), 7.07 - 6.99 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.80 - 4.71 (m, 1H), 4.29 - 4.07 (m, 4H), 3.81 - 3.71 (m, 1H), 3.46 - 3.39 (m, 4H), 2.83 - 2.75 (m, 5H), 2.66 - 2.64 (m, 2H), 2.30 - 2.21 (m, 3H), 1.68 - 1.56 (m,

2H), 1.23 - 0.97 (m, 9H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.68 min, m/z = 604.2 $[M+H]^+$; HPLC (Method A): Rt = 4.73 min, 99.27%.

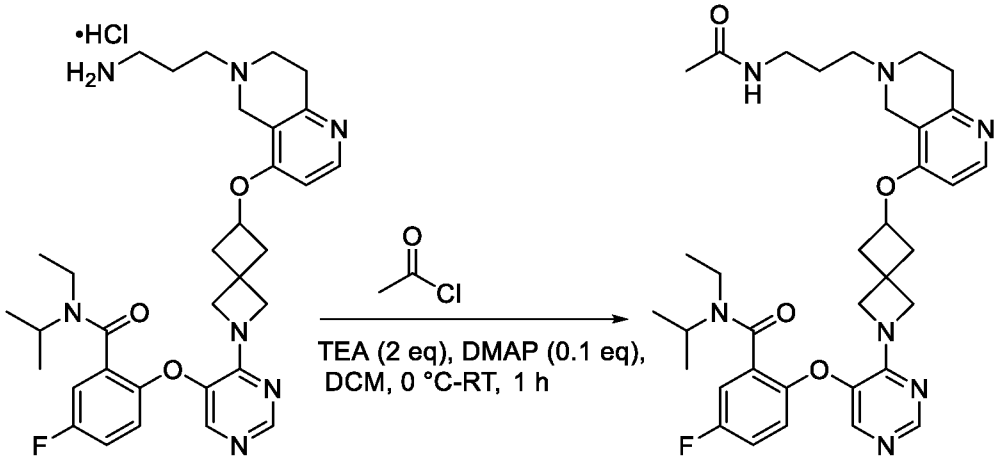
Example 250. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylsulfonamido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 127)



In a dried, 50 mL round bottom flask under nitrogen atmosphere, 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.2 g, 0.312 mmol) was added in DCM (3 mL). To this solution, TEA (0.087 mL, 0.625 mmol) and methanesulfonyl chloride (0.024 mL, 0.312 mmol) were added at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (20% MeOH in DCM). Water (10 mL) was added to the reaction and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylsulfonamido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (60.11 mg, 26.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.09 - 7.00 (m, 1H), 6.98 (t, J = 5.8 Hz, 1H), 6.69 - 6.65 (m, 1H), 4.79 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.75 (spt, J = 6.5 Hz, 1H), 3.43 (s, 2H), 3.40 - 3.37 (m, 1H), 3.28 - 3.11 (m, 2H), 3.00 (q, J = 6.6 Hz, 2H), 2.88 (s, 3H), 2.83 - 2.75 (m, 4H), 2.69 - 2.66 (m, 2H), 2.57 - 2.54 (m, 1H), 2.31 - 2.18 (m, 2H), 1.70 (quin, J = 6.8 Hz, 2H), 1.23 - 0.98 (m, 9H); LCMS

(Method G): Rt = 1.66 min, m/z = 682.4 $[M+H]^+$; HPLC (Method A): Rt = 5.07 min, 99.95%.

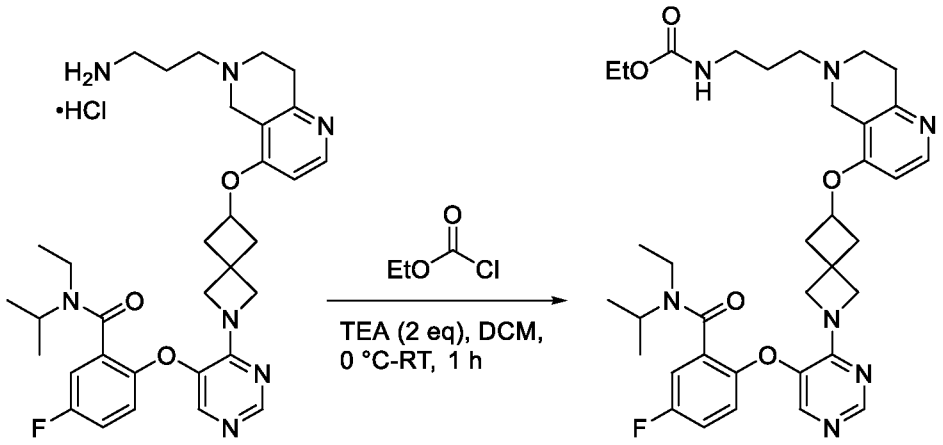
Example 251. 2-((4-(6-((6-(3-Acetamidopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 120)



This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 1 equivalent of acetyl chloride and 0.1 equivalent of DMAP were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((4-(6-((6-(3-acetamidopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 54.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.83 (t, J = 5.2 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.70 - 6.65 (m, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.07 (m, 4H), 3.76 (spt, J = 6.6 Hz, 1H), 3.42 (s, 2H), 3.40 - 3.36 (m, 1H), 3.28 - 3.13 (m, 2H), 3.07 (q, J = 6.6 Hz, 2H), 2.83 - 2.73 (m, 4H), 2.68 - 2.63 (m, 2H), 2.47 - 2.45 (m, 1H), 2.31 - 2.22 (m, 2H), 1.79 (s, 3H), 1.63 (quin, J = 7.0 Hz, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.51 min, m/z = 646.6 $[M+H]^+$; HPLC (Method A): Rt = 4.55 min, 99.08%.

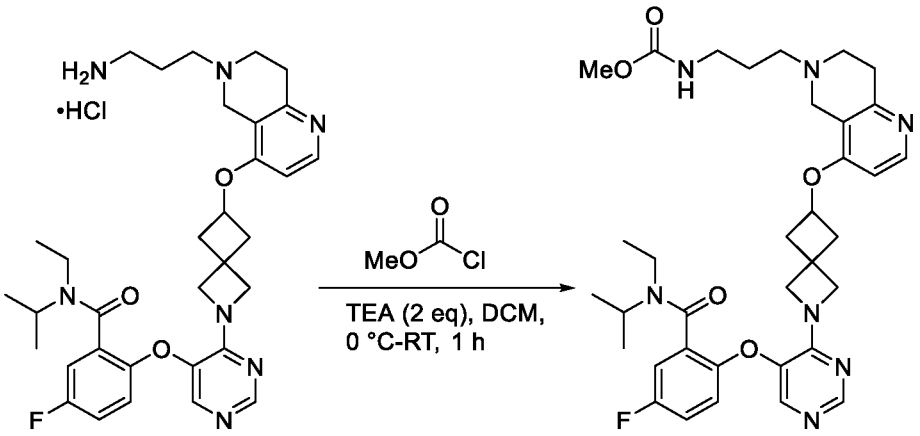
Example 252. Ethyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate (Compound No. 137)



This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 1 equivalent of ethyl chloroformate was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain ethyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate.

Yield: 18.29%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 7.01 (m, 2H), 6.66 (d, J = 5.6 Hz, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.97 (q, J = 7.1 Hz, 2H), 3.76 (spt, J = 6.6 Hz, 1H), 3.41 (s, 2H), 3.40 - 3.34 (m, 1H), 3.28 - 3.11 (m, 2H), 3.03 (q, J = 6.6 Hz, 2H), 2.84 - 2.73 (m, 4H), 2.69 - 2.64 (m, 2H), 2.49 - 2.43 (m, 1H), 2.31 - 2.19 (m, 2H), 1.63 (quin, J = 6.8 Hz, 2H), 1.23 - 0.95 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.73 min, m/z = 676.6 $[M+H]^+$; HPLC (Method A): Rt = 5.47 min, 99.44%.

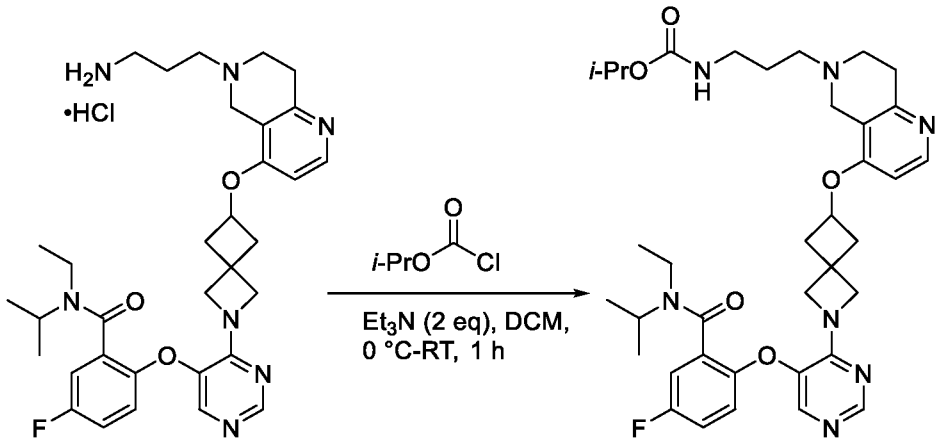
Example 253. Methyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate (Compound No. 138)



This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 1 equivalent of methyl chloroformate was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford methyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate.

Yield: 18.58%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.24 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.65 (m, 1H), 7.35 - 7.20 (m, 2H), 7.12 (t, J = 5.3 Hz, 1H), 7.09 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.75 (quin J = 6.6 Hz, 1H), 3.51 (s, 3H), 3.41 (s, 2H), 3.40 - 3.34 (m, 1H), 3.29 - 3.10 (m, 2H), 3.03 (q, J = 6.5 Hz, 2H), 2.83 - 2.74 (m, 4H), 2.67 - 2.63 (m, 2H), 2.50 - 2.43 (m, 1H), 2.31 - 2.21 (m, 2H), 1.63 (quin, J = 6.9 Hz, 2H), 1.23 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.98 min, m/z = 662.4 $[M+H]^+$; HPLC (Method A): Rt = 5.25 min, 99.96%.

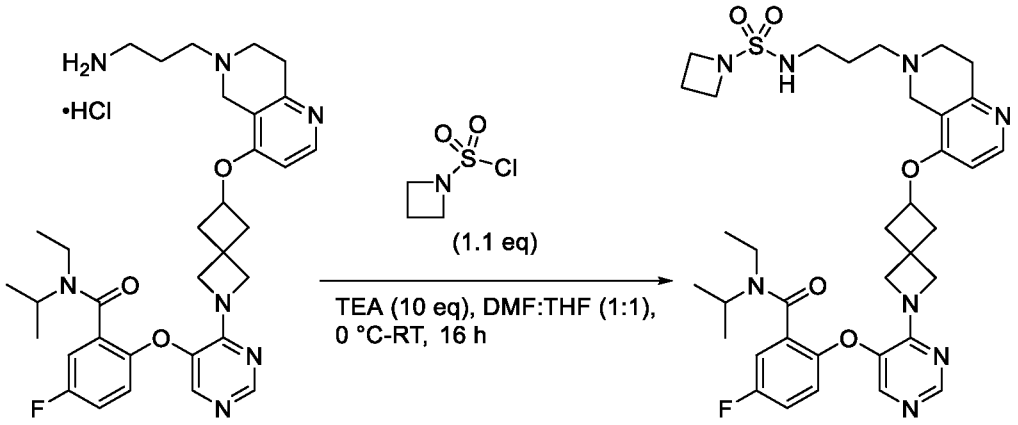
Example 254. Isopropyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate (Compound No. 139)



This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 1 equivalent of isopropyl chloroformate was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford isopropyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)carbamate.

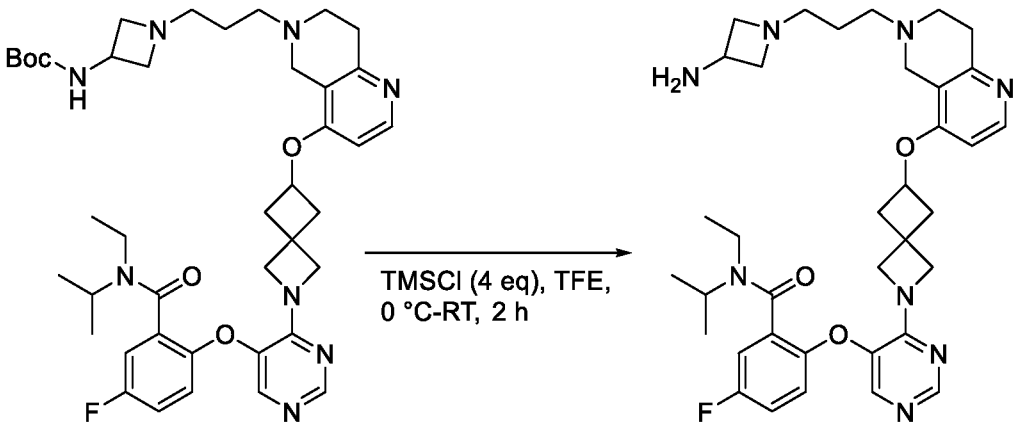
Yield: 42.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.34 - 7.20 (m, 2H), 7.10 - 6.96 (m, 2H), 6.69 - 6.64 (m, 1H), 4.80 - 4.69 (m, 2H), 4.46 - 4.06 (m, 4H), 3.76 (quin J = 6.6 Hz, 1H), 3.41 (s, 2H), 3.40 - 3.35 (m, 1H), 3.28 - 3.11 (m, 2H), 3.02 (q, J = 6.4 Hz, 2H), 2.84 - 2.75 (m, 4H), 2.67 - 2.63 (m, 2H), 2.49 - 2.46 (m, 1H), 2.32 - 2.21 (m, 2H), 1.63 (quin, J = 6.8 Hz, 2H), 1.15 (d, J = 6.3 Hz, 6H), 1.13 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.81 min, m/z = 690.6 $[M+H]^+$; HPLC (Method A): Rt = 5.58 min, 99.93%.

Example 255. 2-((4-(6-((6-(3-(Azetidine-1-sulfonamido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 162)



In a dried, 50 mL round bottom flask under a nitrogen atmosphere, 2-((4-(6-((6-(3-aminopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.3 g, 0.469 mmol) was added in DMF (2 mL) and THF (2 mL). To this solution, TEA (0.653 mL, 4.69 mmol) and azetidine-1-sulfonyl chloride (0.080 g, 0.515 mmol) were added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (20% MeOH in DCM). The reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method F) to obtain 2-((4-(6-((6-(3-(azetidine-1-sulfonamido)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (54 mg, 15.92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.20 - 8.16 (m, 1H), 7.78 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.15 (t, J = 5.7 Hz, 1H), 7.10 - 6.99 (m, 1H), 6.70 - 6.65 (m, 1H), 4.80 - 4.70 (m, 1H), 4.47 - 4.06 (m, 4H), 3.80 - 3.72 (m, 1H), 3.69 (t, J = 7.6 Hz, 4H), 3.43 (s, 2H), 3.42 - 3.35 (m, 1H), 3.29 - 3.10 (m, 2H), 3.00 (q, J = 6.7 Hz, 2H), 2.84 - 2.75 (m, 4H), 2.68 - 2.64 (m, 2H), 2.56 - 2.52 (m, 1H), 2.30 - 2.21 (m, 2H), 2.16 - 2.05 (m, 2H), 1.69 (quin, J = 6.9 Hz, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method A): Rt = 2.34 min, m/z = 723.4 $[M+H]^+$; HPLC (Method D): Rt = 2.47 min, 99.19%.

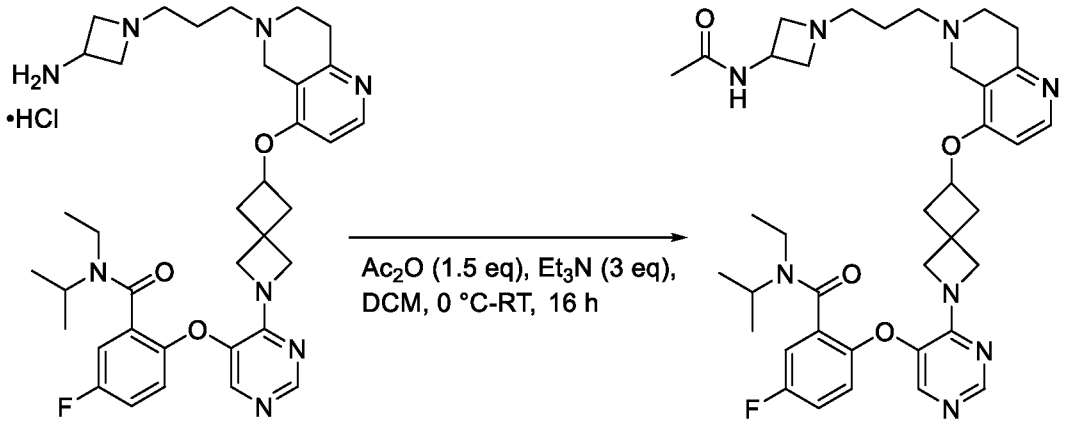
Example 256. 2-((4-(6-((6-(3-(3-Aminoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 154)



In a dried, 100 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate (0.380 g, 0.501 mmol) was added in 2,2,2-trifluoroethanol (10 mL). TMSCl (0.254 mL, 2.003 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain crude 2-((4-(6-((6-(3-(3-aminoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (400 mg, quantitative yield) as a solid. LCMS (Method B): Rt = 1.27 min, m/z = 659.5 $[M+H]^+$; 88.92%. The crude product (250 mg) was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the product. ^{1}HNMR showed impurity peaks. Therefore, the impure product was diluted with water (2 mL) and basified with saturated sodium bicarbonate, extracted with 10% MeOH in DCM (3 x 10 mL). The combined organic layer dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure and lyophilized to obtain 2-((4-(6-((6-(3-(3-aminoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 33.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.63 (m, 1H), 4.79 - 4.69 (m, 1H), 4.45 - 4.08 (m, 4H), 3.82 - 3.69 (m, 1H), 3.53 - 3.41 (m, 3H), 3.38 (s, 2H), 3.27 - 3.11 (m, 2H), 2.82 - 2.76 (m, 4H), 2.66 - 2.62 (m, 2H), 2.48 - 2.44 (m, 4H), 2.36 - 2.31 (m, 2H), 2.29 - 2.23 (m, 2H), 1.47 (quin, J = 7.1 Hz, 2H), 1.23 - 0.98 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.59 min, m/z = 659.3 $[M+H]^+$; HPLC (Method A): Rt = 5.10 min, 98.45%.

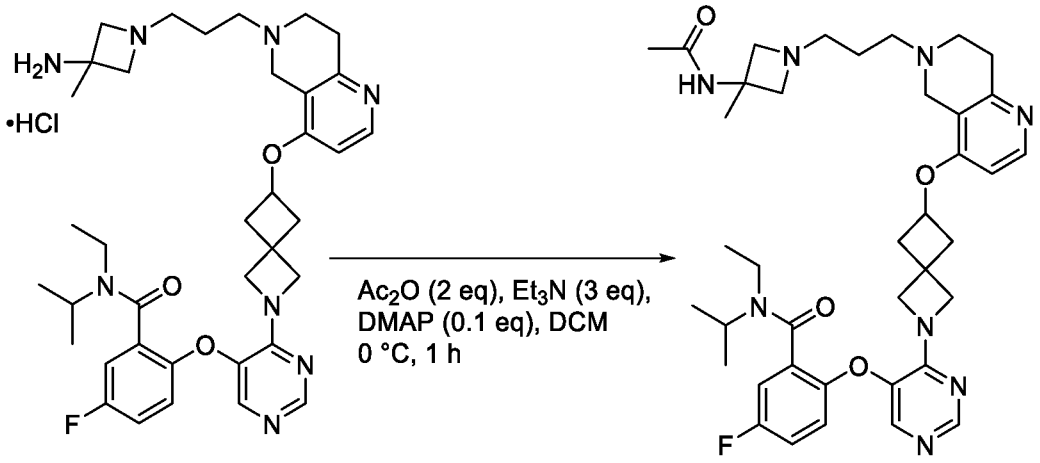
Example 257. 2-((4-(6-((6-(3-(3-Acetamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 164)



This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 1 equivalent of 2-((4-(6-((6-(3-(3-aminoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 1.5 equivalents of acetic anhydride, except that 3 equivalents of Et_3N was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by achiral Prep SFC (Method C) to obtain 2-((4-(6-((6-(3-(3-acetamidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 11.22%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.27 (m, 1H), 8.27 - 8.22 (m, 1H), 8.20 - 8.16 (m, 1H), 7.76 - 7.67 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.45 - 4.08 (m, 5H), 3.83 - 3.69 (m, 1H), 3.46 (t, J = 7.2 Hz, 2H), 3.44 - 3.40 (m, 1H), 3.39 (s, 2H), 3.27 - 3.11 (m, 2H), 2.83 - 2.71 (m, 5H), 2.68 - 2.63 (m, 2H), 2.48 - 2.44 (m, 2H), 2.39 (t, J = 7.0 Hz, 2H), 2.30 - 2.22 (m, 2H), 1.78 (s, 3H), 1.49 (quin, J = 7.0 Hz, 2H), 1.22 - 0.98 (m, 9H); LCMS (Method D): Rt = 1.63 min, m/z = 701.5 $[M+H]^+$; HPLC (Method A): Rt = 4.62 min, 98.20%.

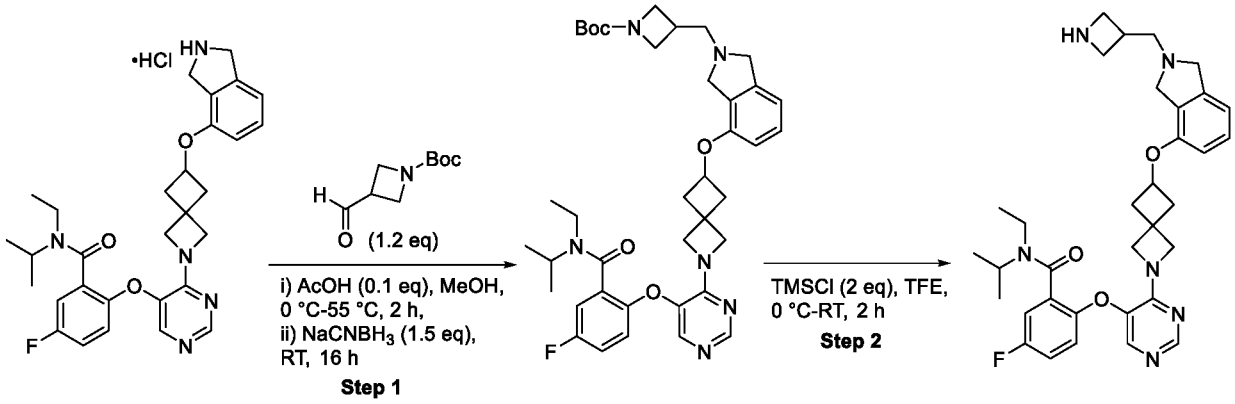
Example 258. 2-((4-(6-((6-(3-(3-Acetamido-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 188)



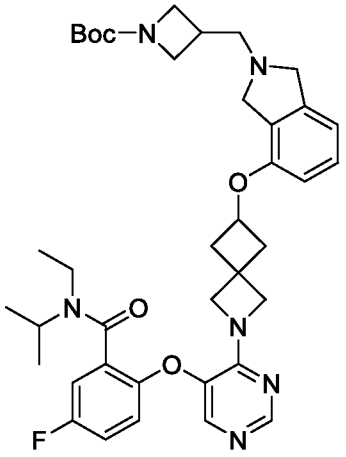
This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 1 equivalent of 2-((4-(6-((6-(3-(3-amino-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 2 equivalents of acetic anhydride, except that 3 equivalents of Et_3N and 0.1 equivalent of DMAP were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((4-(6-((6-(3-(3-acetamido-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 30.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 8.09 (s, 1H), 7.77 - 7.64 (m, 1H), 7.33 - 7.20 (m, 2H), 7.11 - 6.98 (m, 1H), 6.68 - 6.64 (m, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.08 (m, 4H), 3.82 - 3.68 (m, 1H), 3.45 - 3.40 (m, 1H), 3.39 (br s, 2H), 3.27 - 3.21 (m, 1H), 3.14 (d, J = 7.4 Hz, 2H), 2.97 (d, J = 7.4 Hz, 2H), 2.83 - 2.74 (m, 4H), 2.67 - 2.63 (m, 2H), 2.46 - 2.43 (m, 2H), 2.40 (br t, J = 7.0 Hz, 2H), 2.30 - 2.22 (m, 2H), 1.76 (s, 3H), 1.53 - 1.44 (m, 2H), 1.41 (s, 3H), 1.23 - 0.98 (m, 9H); LCMS (Method D): Rt = 1.64 min, m/z = 715.5 $[M+H]^+$; HPLC (Method A): Rt = 4.59 min, 99.10%.

Example 259. 2-((4-(6-((2-(Azetidin-3-ylmethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 40)



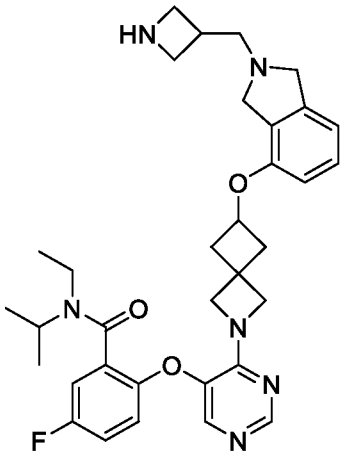
Step 1. tert-Butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1 equivalent of *N*-ethyl-5-fluoro-2-((4-(6-(isoindolin-4-yloxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride, except that 1.2 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, 0.1 equivalent of AcOH, and 1.5 equivalents of $NaCNBH_3$ were used. The imine formation reaction was stirred at 55 °C. After completion, the reaction was added to ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)azetidine-1-carboxylate.

Yield: 36.9%; LCMS (Method D): Rt = 2.37 min, m/z = 701.5 $[M+H]^+$; 91.39%.

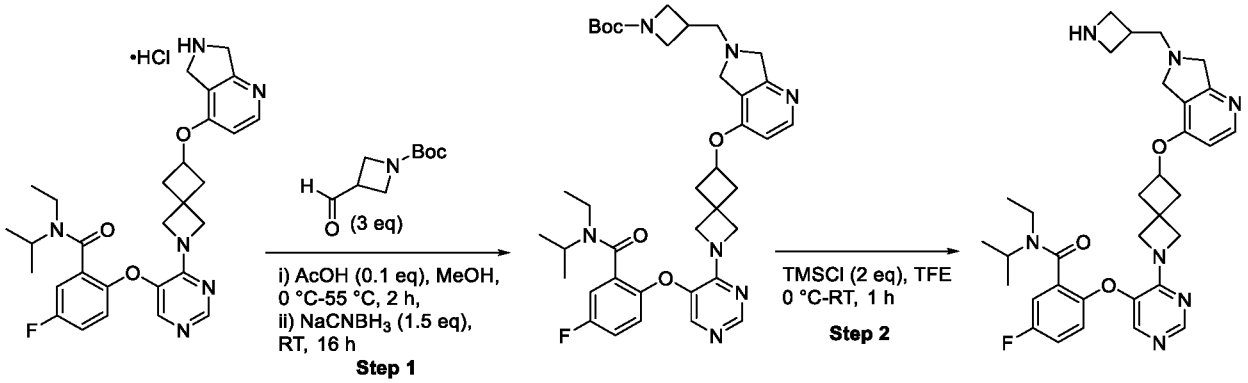
Step 2. 2-((4-(6-((2-(Azetidin-3-ylmethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



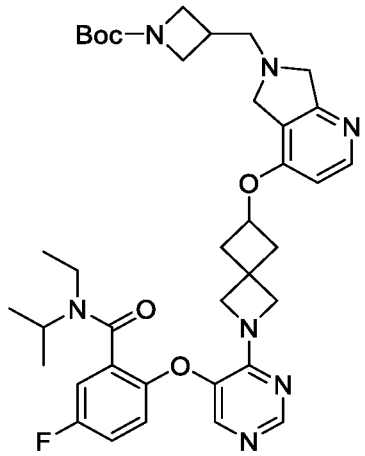
This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindolin-2-yl)methyl)azetidine-1-carboxylate, except that 2 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to obtain crude 2-((4-(6-((2-(azetidin-3-ylmethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude product was triturated with EtOAc, the organic layer was decanted, and the residue was dried under a vacuum. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to obtain 2-((4-(6-((2-(azetidin-3-ylmethyl)isoindolin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 20.71%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.23 (m, 1H), 7.79 - 7.63 (m, 1H), 7.33 - 7.22 (m, 2H), 7.14 - 7.00 (m, 2H), 6.79 (d, J = 7.4 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 4.71 - 4.60 (m, 1H), 4.46 - 4.06 (m, 4H), 3.94 - 3.81 (m, 1H), 3.80 - 3.70 (m, 4H), 3.54 - 3.37 (m, 4H), 3.27 - 3.14 (m, 3H), 2.86 - 2.70 (m, 5H), 2.26 - 2.15 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.52 min, m/z = 601.0 $[M+H]^+$; HPLC (Method A): Rt = 5.21 min, 98.04%.

Example 260. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 47)



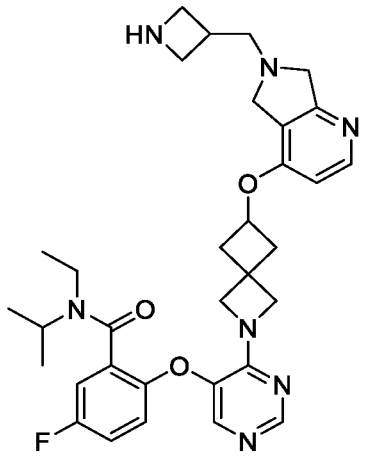
Step 1.tert-Butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)methyl)azetidine-1-carboxylate)



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1 equivalent of 2-((4-(6-((6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (300 mg, 0.527 mmol), except that 3 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, 0.1 equivalent of AcOH, and 1.5 equivalents of $NaCNBH_3$ were used. The imine formation reaction was stirred at 55 °C. After completion, the reaction was added to ice-cold water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)methyl)azetidine-1-carboxylate.

Yield: 6.69%; LCMS (Method D): Rt = 2.06 min, m/z = 703.3 $[M+H]^+$; 41.27%.

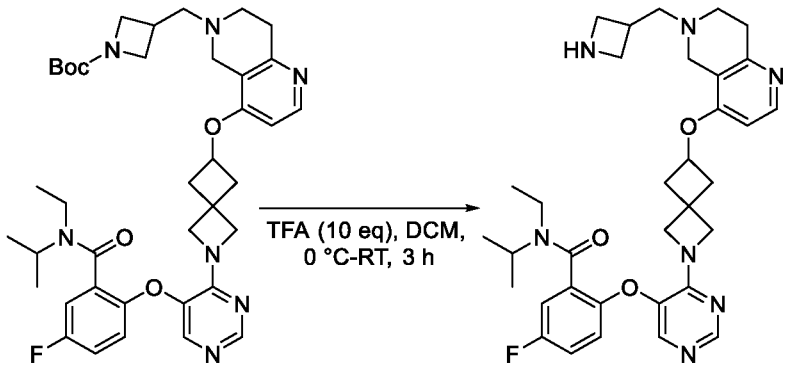
Step 2. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)methyl)azetidine-1-carboxylate, except that 2 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method B) to obtain 2-((4-(6-((6-(azetidin-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

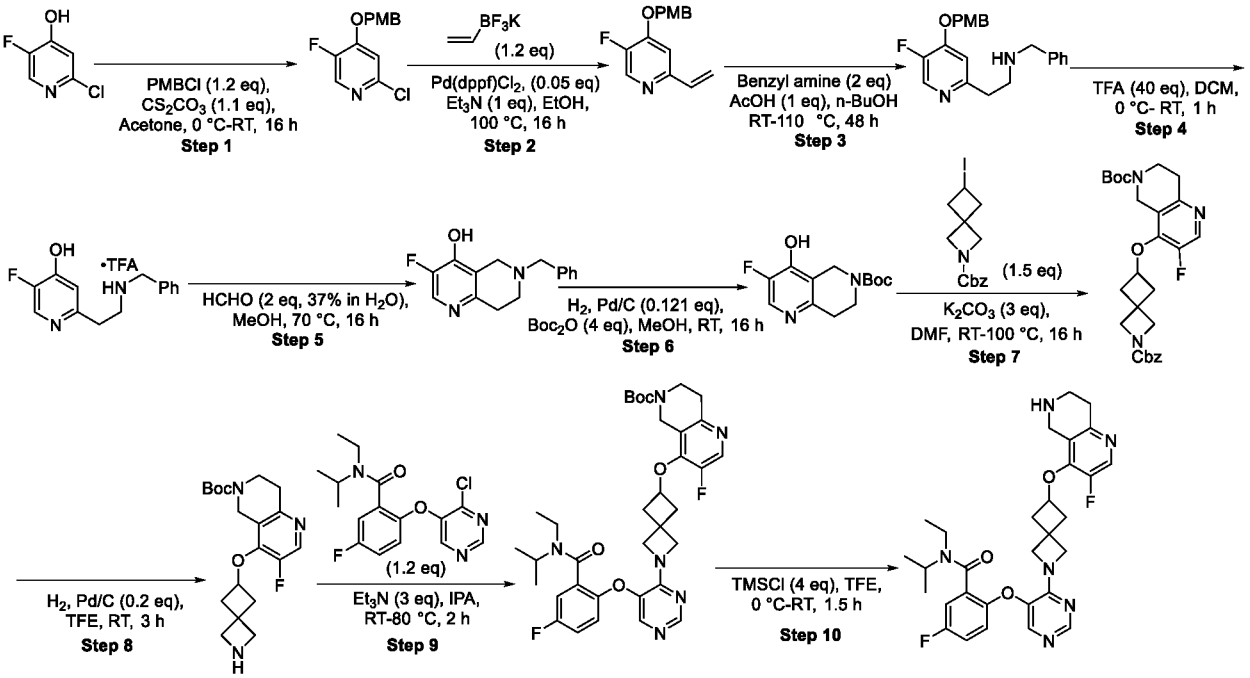
Yield: 17.42%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.19 (d, J = 5.9 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.71 (d, J = 5.8 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.45 - 4.08 (m, 4H), 3.84 - 3.71 (m, 5H), 3.54 - 3.46 (m, 1H), 3.45 - 3.38 (m, 2H), 3.25 - 3.21 (m, 2H), 2.87 - 2.74 (m, 5H), 2.30 - 2.14 (m, 3H), 1.22 - 0.98 (m, 9H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.54 min, m/z = 602.6 $[M+H]^+$; HPLC (Method A): Rt = 5.67 min, 98.98%.

Example 261. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 61)

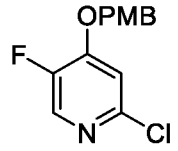


This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate, except that 10 equivalents of TFA was used and DCM was used as a solvent. After completion, the reaction was concentrated under reduced pressure to afford crude 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide trifluoroacetate. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.
Yield: 34.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.49 - 3.84 (m, 5H), 3.75 (spt, J = 6.6 Hz, 1H), 3.54 - 3.46 (m, 2H), 3.41 (m, 3H), 3.26 - 3.22 (m, 3H), 2.83 - 2.73 (m, 4H), 2.73 - 2.61 (m, 5H), 2.31 - 2.16 (m, 2H), 1.38 - 0.81 (m, 9H); LCMS (Method B): Rt = 1.33 min, m/z = 616.4 $[M+H]^+$; HPLC (Method A): Rt = 5.28 min, 98.09%.

Example 262. *N*-Ethyl-5-fluoro-2-((4-(6-((3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide
(Compound No. 192)



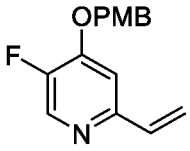
Step 1. 2-Chloro-5-fluoro-4-((4-methoxybenzyl)oxy)pyridine



This compound was synthesized following the procedure described for the synthesis of Intermediate 9, step 1, starting with 1 equivalent of 2-chloro-5-fluoropyridin-4-ol. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain 2-chloro-5-fluoro-4-((4-methoxybenzyl)oxy)pyridine as a solid.

Yield: 7.37%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 2.7 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.02 - 6.92 (m, 3H), 5.12 (s, 2H), 3.85 (s, 3H); LCMS (Method G): Rt = 1.97 min, m/z = 268.2 $[M+H]^+$, 83.22%.

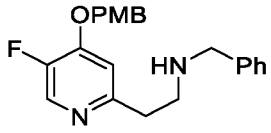
Step 2. 5-Fluoro-4-((4-methoxybenzyl)oxy)-2-vinylpyridine



This compound was synthesized following the procedure described for the synthesis of Intermediate 10, step 1, starting with 2-chloro-5-fluoro-4-((4-methoxybenzyl)oxy)pyridine. The crude was purified by flash column chromatography using EtOAc and hexane (product was eluted at 20% EtOAc in hexane) to obtain 5-fluoro-4-((4-methoxybenzyl)oxy)-2-vinylpyridine as a solid.

Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 3.0 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.02 (d, *J* = 6.7 Hz, 1H), 6.98 - 6.91 (m, 2H), 6.74 (dd, *J* = 10.8, 17.4 Hz, 1H), 6.08 (d, *J* = 17.4 Hz, 1H), 5.47 (d, *J* = 10.9 Hz, 1H), 5.16 (s, 2H), 3.85 (s, 3H); LCMS (Method D): Rt = 2.08min, m/z = 260.1 $[M+H]^+$, 98.81%.

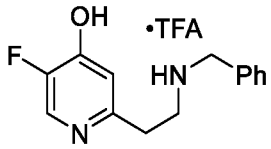
Step 3. N-Benzyl-2-(5-fluoro-4-((4-methoxybenzyl)oxy)pyridin-2-yl)ethan-1-amine



This compound was synthesized following the procedure described for the synthesis of Intermediate 10, step 2, starting with 5-fluoro-4-((4-methoxybenzyl)oxy)-2-vinylpyridine, except that *n*-butanol solvent was used. The reaction was stirred at 110 °C. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 7% MeOH in DCM) to obtain *N*-benzyl-2-(5-fluoro-4-((4-methoxybenzyl)oxy)pyridin-2-yl)ethan-1-amine as a semi-solid.

Yield: 38.2%; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 8.28 (d, *J* = 3.2 Hz, 1H), 7.44 - 7.39 (m, 2H), 7.33 - 7.28 (m, 4H), 7.28 - 7.15 (m, 2H), 7.00 - 6.93 (m, 2H), 5.16 (s, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 2.83 (br s, 4H), 2.18 (br s, 1H); LCMS (Method G): Rt = 2.00 min, m/z = 367.3 $[M+H]^+$, 99.01%.

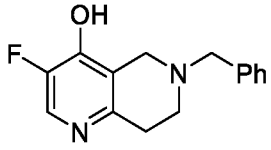
Step 4. 2-(2-(Benzylamino)ethyl)-5-fluoropyridin-4-ol 2,2,2-trifluoroacetic acid



This compound was synthesized following the procedure described for the synthesis of Intermediate 10, step 3, starting with *N*-benzyl-2-(5-fluoro-4-((4-methoxybenzyl)oxy)pyridin-2-yl)ethan-1-amine. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain 2-(2-(benzylamino)ethyl)-5-fluoropyridin-4-ol 2,2,2-trifluoroacetic acid as a semi-solid.

Yield: 67.4%; LCMS (Method D): Rt = 1.22 min, m/z = 247.1 $[M+H]^+$, 99.40%.

Step 5. 6-Benzyl-3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol)

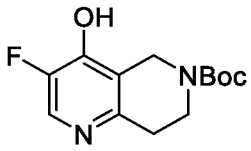


This compound was synthesized following the procedure described for the synthesis of Example 31, step 4, starting with 2-(2-(benzylamino)ethyl)-5-fluoropyridin-4-ol 2,2,2-

trifluoroacetic acid, except that 2 equivalents of formaldehyde (37% in H_2O) was used. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 15% MeOH in DCM) to obtain 6-benzyl-3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol as a solid.

Yield: 90%; ^{1}H NMR (400 MHz, methanol-d_4): δ 8.01 (d, J = 6.0 Hz, 1H), 7.60 - 7.55 (m, 2H), 7.55 - 7.50 (m, 3H), 4.47 (s, 2H), 4.13 (br s, 2H), 3.56 (br s, 2H), 3.12-3.09 (m, 2H), -OH proton not observed; LCMS (Method G): Rt = 1.20 min, m/z = 259.2 $[M+H]^+$, 99.42%.

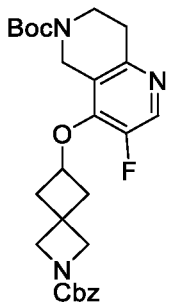
Step 6. tert-Butyl 3-fluoro-4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 31, step 5, starting with 6-benzyl-3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (500 mg, 1.936 mmol), except that, 0.121 equivalent of Pd/C and 4 equivalents of $(Boc)_2O$ were used. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain *tert*-butyl 3-fluoro-4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 33.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91-7.84 (m, 1H), 4.40 (br s, 2H), 3.69 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 1.48 (s, 9H), -OH proton was not observed; LCMS (Method D): Rt = 1.30 min, m/z = 269.0 $[M+H]^+$, 84.53%.

Step 7. tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

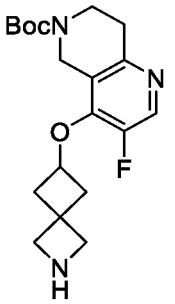


This compound was synthesized following the procedure described for the synthesis of Example 31, step 6, starting with 1.5 equivalents of benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of *tert*-butyl 3-fluoro-4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate was used. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain

tert-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 81%; LCMS (Method D): Rt = 1.48 min, m/z = 496.1 [M-H]-, 97.41%.

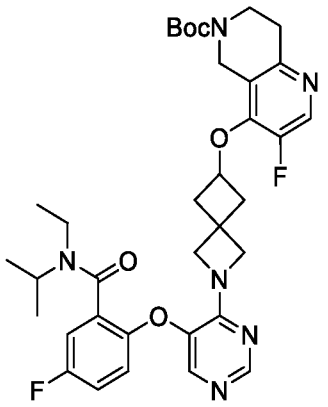
Step 8. tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 31, step 7, starting with *tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 0.2 equivalent of Pd/C was used. The reaction was concentrated under reduced pressure to obtain *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a semi-solid. This material was used without further purification.

Yield: 91%; LCMS (Method D): Rt = 1.62 min, m/z = 364.2 $[M+H]^+$, 98.21%.

Step 9. tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

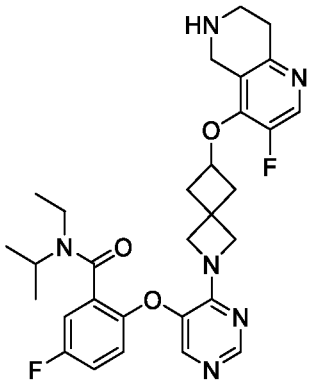


This compound was synthesized following the procedure described for the synthesis of Example 31, step 8, starting with 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that *tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one

(Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a semi-solid.

Yield: 48.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, J = 3.9 Hz, 1H), 8.30 - 8.24 (m, 1H), 7.76 - 7.61 (m, 1H), 7.33 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 4.98 - 4.86 (m, 1H), 4.44 (s, 2H), 4.27 - 4.08 (m, 4H), 3.79 - 3.69 (m, 1H), 3.61 (t, J = 6.0 Hz, 2H), 3.48 - 3.30 (m, 2H), 2.79 (t, J = 6.0 Hz, 2H), 2.72 - 2.63 (m, 2H), 2.40 - 2.28 (m, 2H), 1.43 (s, 9H), 1.29 - 0.80 (m, 9H); LCMS (Method D): Rt = 2.21 min, m/z = 665.4 $[M+H]^+$, 97.79%.

Step 10. N-Ethyl-5-fluoro-2-((4-(6-((3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

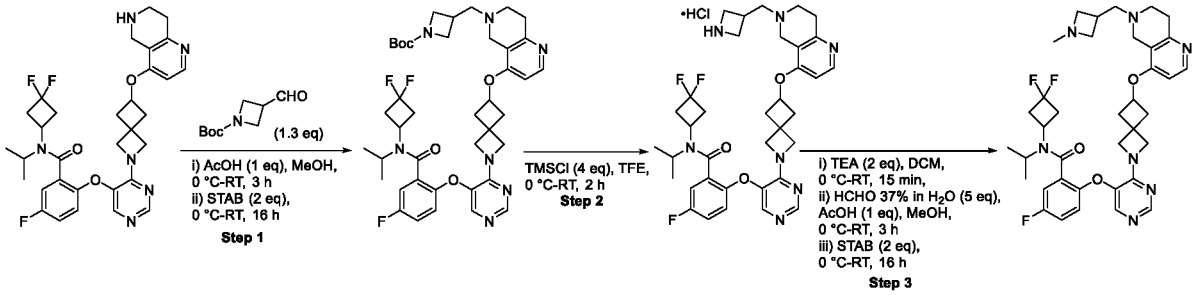


This compound was synthesized following the procedure described for the synthesis of Example 31, step 9, starting with *tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3-fluoro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-2-((4-(6-((3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((3-fluoro-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

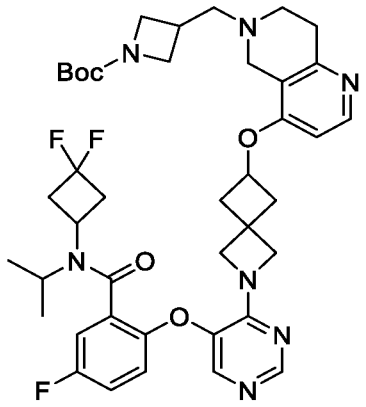
Yield: 59.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.27 - 8.24 (m, 1H), 7.81 - 7.64 (m, 1H), 7.36 - 7.20 (m, 2H), 7.09 - 6.99 (m, 1H), 4.90 - 4.80 (m, 1H), 4.27 - 4.05 (m, 4H), 3.83 - 3.67 (m, 3H), 3.51 - 3.20 (m, 2H), 2.94 (t, J = 5.9 Hz, 2H), 2.71 - 2.59 (m, 4H), 2.39 - 2.24 (m, 2H), 1.24 - 0.91 (m, 9H), one proton merged with solvent peaks; LCMS

(Method D): Rt = 1.69 min, m/z = 565.3 $[M+H]^+$; HPLC (Method A): Rt = 4.90 min, 99.94%.

Example 263. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 266)



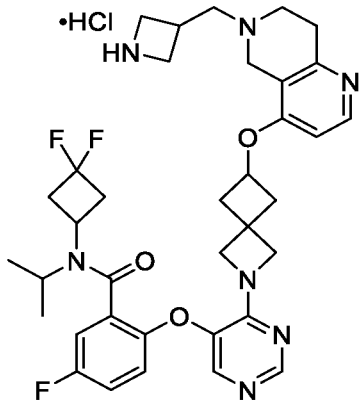
Step 1. tert-Butyl 3-((4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.3 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, 1 equivalent of AcOH and 2 equivalents of STAB were used. After completion, the reaction was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 6% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate as a solid.

Yield: 63.4%; LCMS (Method G): Rt = 2.18 min, m/z = 778.7 $[M+H]^+$; 87.27%

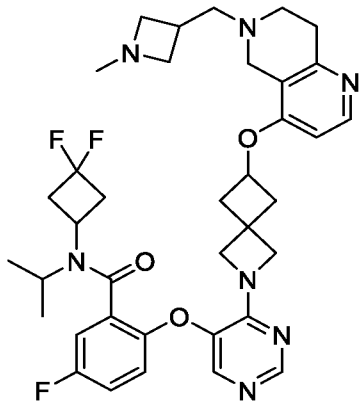
Step 2. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(5-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc. The organic layer was decanted, and the solid was dried under a vacuum to obtain 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide hydrochloride as a solid.

Yield: 99%; LCMS (Method G): Rt = 1.75 min, m/z = 678.3 $[M+H]^+$; 84.60%

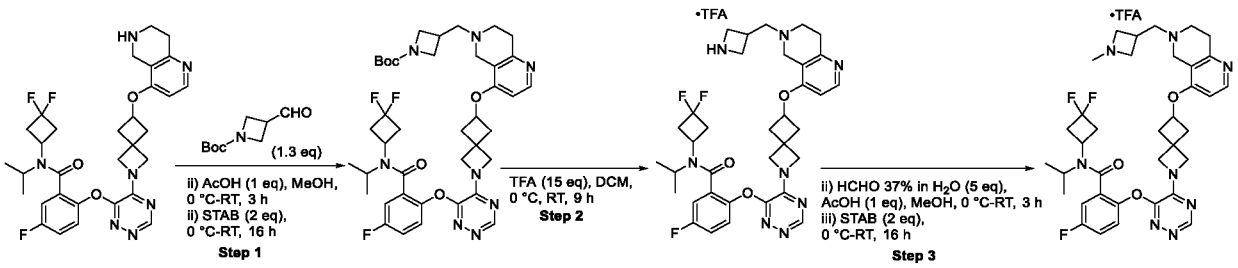
Step 3. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



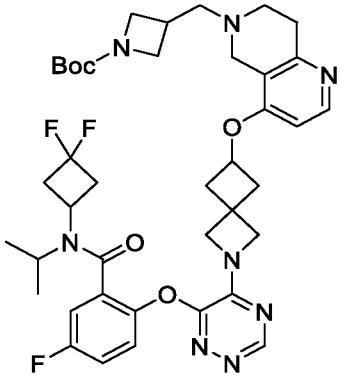
In a 50 mL single neck round bottom flask under a nitrogen atmosphere, 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.3 g, 0.420 mmol) was added in DCE (3 mL). Et_3N (0.117 mL, 0.840 mmol) was added to this solution at 0 °C, and the reaction was stirred for 15 min at RT. The reaction was concentrated under reduced pressure. To this crude material, MeOH (2.5 mL) was added, then formaldehyde (0.156 mL, 2.100 mmol, 37% in H_2O) and AcOH (0.024 mL, 0.420 mmol) were added at 0 °C. The reaction was stirred at RT for 3 h. To this mixture, sodium triacetoxyborohydride (0.178 g, 0.840 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was diluted with water (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AM) to afford *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (47.21mg, 15.97% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 (s, 1H), 7.40 - 7.33 (m, 1H), 7.32 - 7.23 (m, 1H), 7.06 (br dd, J = 4.3, 9.0 Hz, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.74 (quin, J = 6.5 Hz, 1H), 4.33 - 4.07 (m, 4H), 3.96 - 3.85 (m, 1H), 3.79 - 3.74 (m, 2H), 3.60 - 3.49 (m, 1H), 3.37 (br s, 2H), 2.84 - 2.73 (m, 7H), 2.70 - 2.58 (m, 7H), 2.25 (br dd, J = 6.4, 12.8 Hz, 2H), 2.19 (s, 3H), 1.16 - 0.97 (m, 6H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.80 min, m/z = 692.3 $[M+H]^+$; HPLC (Method A): Rt = 5.27 min, 99.70%.

Example 264. *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate

(Compound No. 271-a)



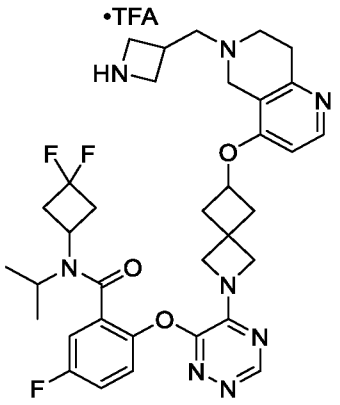
Step 1. tert-Butyl 3-((4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1 equivalent of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 1.3 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, 2 equivalents of STAB and 1 equivalent of AcOH were used. After completion, the reaction was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 6% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate as a gummy liquid.

Yield: 82%; LCMS (Method G): Rt = 2.13 min, m/z = 779.6 $[M+H]^+$; 92.60%.

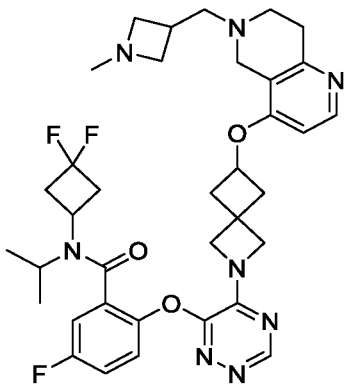
Step 2. 2-((5-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide 2,2,2-trifluoroacetate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate, except that 15 equivalents of TFA was used in lots (lot-1, 10 equivalents and lot-2, 5 equivalents), and DCM was used as a solvent. After completion, the reaction was quenched with saturated sodium bicarbonate solution (temperature was maintained at 0 - 10 °C) and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain crude 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide 2,2,2-trifluoroacetate as a solid. This material was used without further purification.

Yield: 84.64%; LCMS (Method G): Rt = 1.67 min, m/z = 679.6 $[M+H]^+$; 96.70%.

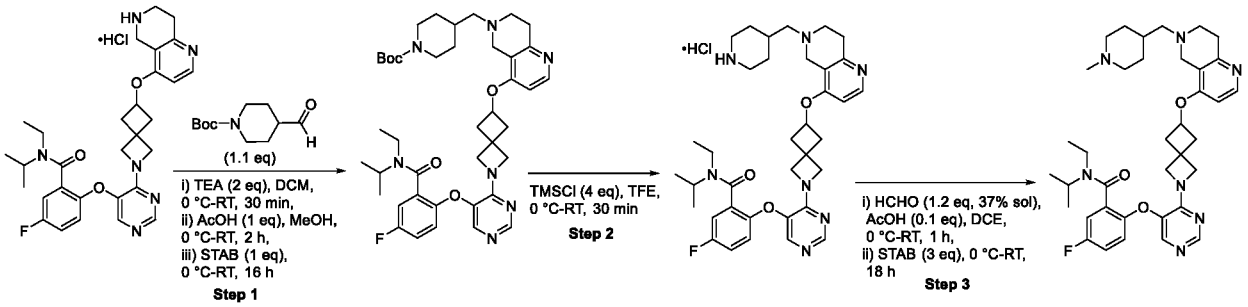
Step 3. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate



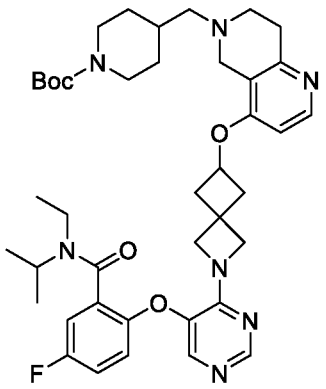
This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide 2,2,2-trifluoroacetate, except that MeOH was used as a solvent. After completion, the reaction was diluted with water and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate as a solid. Yield: 35.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, *J* = 5.5 Hz, 1H), 7.51 - 7.35 (m, 3H), 6.70 - 6.64 (m, 1H), 4.79 (quin, *J* = 6.6 Hz, 1H), 4.66 - 4.50 (m, 2H), 4.28 - 4.13 (m, 2H), 3.90 - 3.80 (m, 1H), 3.68 - 3.58 (m, 1H), 3.38 (br s, 2H), 2.87 - 2.62 (m, 15H), 2.36 - 2.29 (m, 2H), 2.17 (br s, 3H), 1.46 - 0.67 (m, 6H), two protons merged with solvent peaks; ^{19}F NMR (377 MHz, DMSO-d_6): δ -73.40 (s, 3F), -80.99 (d, *J* = -201.32 Hz, 1F), -96.21 (d, *J* = -202.45 Hz, 1F), -116.08 (s, 1F); LCMS (Method G): Rt = 1.75 min, m/z = 693.7 $[M+H]^+$; HPLC (Method A): Rt = 5.01 min, 99.66%.

Example 265. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylpiperidin-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 80)

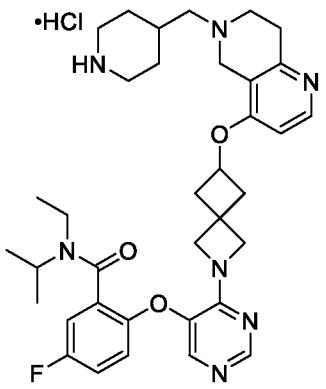


Step 1. tert-Butyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)piperidine-1-carboxylate



In a dried, 50 mL two neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (300 mg, 0.514 mmol) in DCM (3 mL), Et_3N (0.143 mL, 1.029 mmol) was added at 0 °C. The reaction was stirred at RT for 30 min. The reaction was concentrated under reduced pressure and diluted with MeOH (5 mL) at 0 °C. To this reaction mixture, *tert*-butyl 4-formylpiperidine-1-carboxylate (121 mg, 0.566 mmol) and AcOH (0.029 mL, 0.514 mmol) were added, and the reaction was stirred at RT for 2 h. To this mixture, sodium triacetoxyborohydride (109 mg, 0.514 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was concentrated under reduced pressure, quenched with ice water (20 mL), and extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 2-5% MeOH in DCM) to obtain *tert*-butyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)piperidine-1-carboxylate (85 mg, 22.21% yield) as a solid. LCMS (Method G): Rt = 2.17 min, m/z = 744.7 $[M+H]^+$; 84.36%.

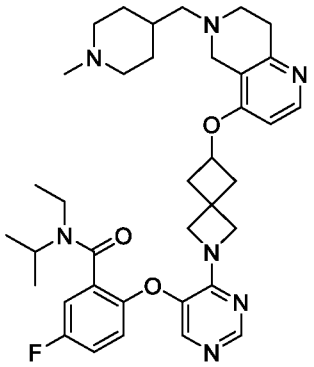
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(piperidin-4-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)piperidine-1-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(3-methyl-3-(2-((6-(piperidin-4-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)ethyl)azetidin-1-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride as a solid. This material was used without further purification.

Yield: 63.7%; LCMS (Method G): Rt = 1.63 min, m/z = 644.4 $[M+H]^+$, 76.20%.

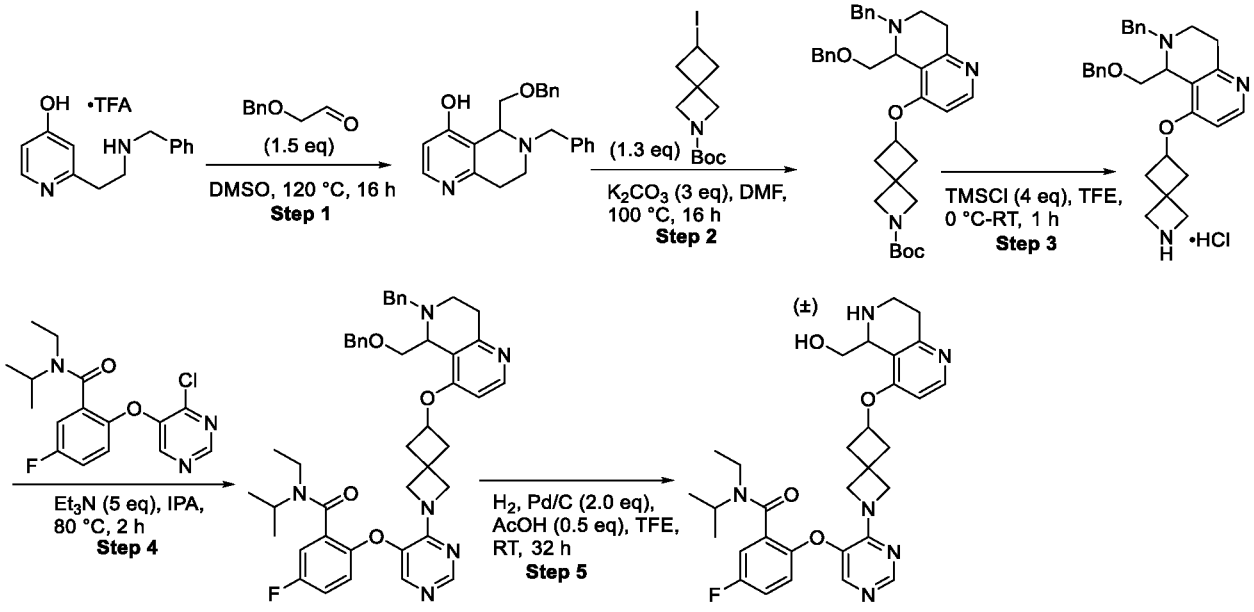
Step 3. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpiperidin-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



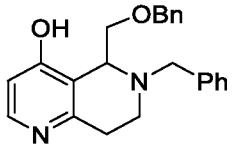
This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(piperidin-4-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except 1.2 equivalents of formaldehyde (37% in H_2O), 0.1 equivalent of AcOH, and 3 equivalents of STAB were used. After completion, the reaction was diluted with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and

the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylpiperidin-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 40.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.32 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.45 - 4.09 (m, 4H), 3.81 - 3.71 (m, 1H), 3.44 - 3.35 (m, 3H), 3.27 - 3.11 (m, 2H), 2.83 - 2.69 (m, 6H), 2.67 - 2.63 (m, 2H), 2.35 - 2.21 (m, 4H), 2.14 (s, 3H), 1.84 (br t, J = 10.8 Hz, 2H), 1.67 (br d, J = 11.6 Hz, 2H), 1.54 - 1.50 (m, 1H), 1.25 - 0.97 (m, 9H); one proton merged with solvent peak; LCMS (Method A): Rt = 2.26 min, m/z = 658.5 $[M+H]^+$; HPLC (Method A): Rt = 5.12 min, 97.54%.

Example 266. (±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 251)



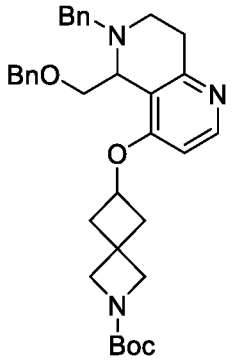
Step 1. (±)-6-Benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (3 g, 8.76 mmol) in DMSO (75 mL), 2-(benzyloxy)acetaldehyde (1.847 mL, 13.15 mmol) was added at RT. The reaction was stirred at 120 °C for 16 h. The reaction progress was

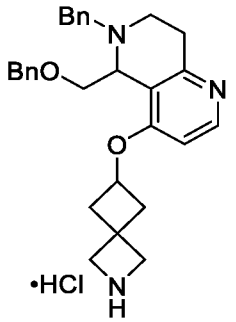
monitored by TLC (20% MeOH in DCM). After completion, the reaction was diluted with water (70 mL) and extracted with DCM (3 x 100 mL). The combined organic layer was washed with brine solution (50 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 6% MeOH in DCM) to afford (±)-6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (570 mg, 16.24% yield) as a liquid. LCMS (Method G): Rt = 1.68 min, m/z = 361.3 $[M+H]^+$; 90.04%.

Step 2. (±)-tert-Butyl 6-((6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



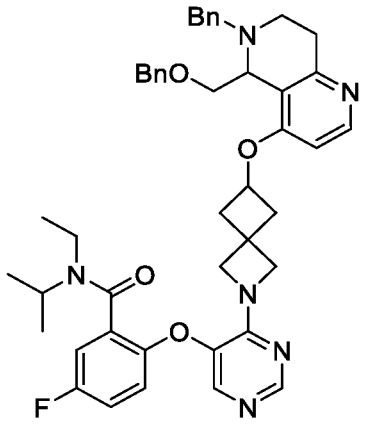
To a stirred solution of (±)-6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (0.57 g, 1.581 mmol) in DMF (17.2 mL), powdered K_2CO_3 (0.656 g, 4.74 mmol) and *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (0.664 g, 2.056 mmol) were added at RT. The reaction was stirred at 100 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with water (50 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with cold water (3 x 50 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 10% MeOH in DCM) to afford (±)-*tert*-butyl 6-((6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.47 g, 40.4% yield) as a solid. LCMS (Method G): Rt = 2.75 min, m/z = 556.6 $[M+H]^+$;75.48%.

Step 3. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



In a 50 mL round bottom flask under nitrogen atmosphere, (±)-*tert*-butyl 6-((6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.46 g, 0.828 mmol) was dissolved in 2,2,2-trifluoroethanol (3 mL). TMSCl (0.423 ml, 3.31 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc (2 x 10 mL). The organic layer was decanted, and the solid was dried under reduced pressure to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (0.42 g, 92% yield) as a solid. LCMS (Method G): Rt = 2.18 min, m/z = 456.2 $[M+H]^+$; 89.12%. This material was used without further purification.

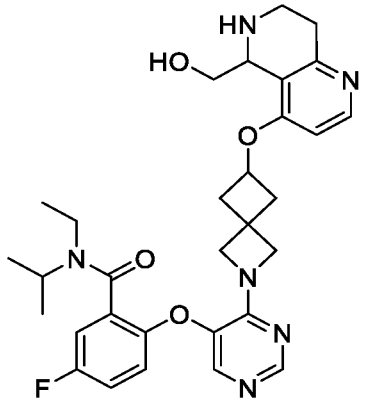
Step 4. (±)-2-((4-(6-((6-Benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a stirred solution of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (0.42 g, 0.854 mmol) in 2-propanol (10 mL), TEA (0.595 mL, 4.27 mmol) and 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.288 g, 0.854 mmol) were added at RT. The reaction was stirred at 80 °C for 2 h. The reaction progress was monitored by TLC (10%

MeOH in DCM). After completion, the reaction was diluted with water (50 mL) and extracted with 10% MeOH in DCM (2 x 100 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 8% MeOH in DCM) to afford (±)-2-((4-(6-((6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.37 g, 55.0% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.77 - 7.67 (m, 1H), 7.40 - 7.20 (m, 12H), 7.11 - 7.03 (m, 1H), 6.69 (d, J = 5.5 Hz, 1H), 4.76 - 4.65 (m, 1H), 4.49 (s, 2H), 4.42 - 4.04 (m, 5H), 3.87 (br d, J = 13.9 Hz, 1H), 3.81 - 3.66 (m, 3H), 3.61 - 3.48 (m, 1H), 3.44 - 3.37 (m, 1H), 3.28 - 3.10 (m, 2H), 2.94 - 2.77 (m, 2H), 2.77 - 2.66 (m, 2H), 2.60 - 2.57 (m, 1H), 2.18 - 2.00 (m, 2H), 1.25 - 0.94 (m, 9H); LCMS (Method G): Rt = 2.35 min, m/z = 757.7 $[M+H]^+$; 96.42%.

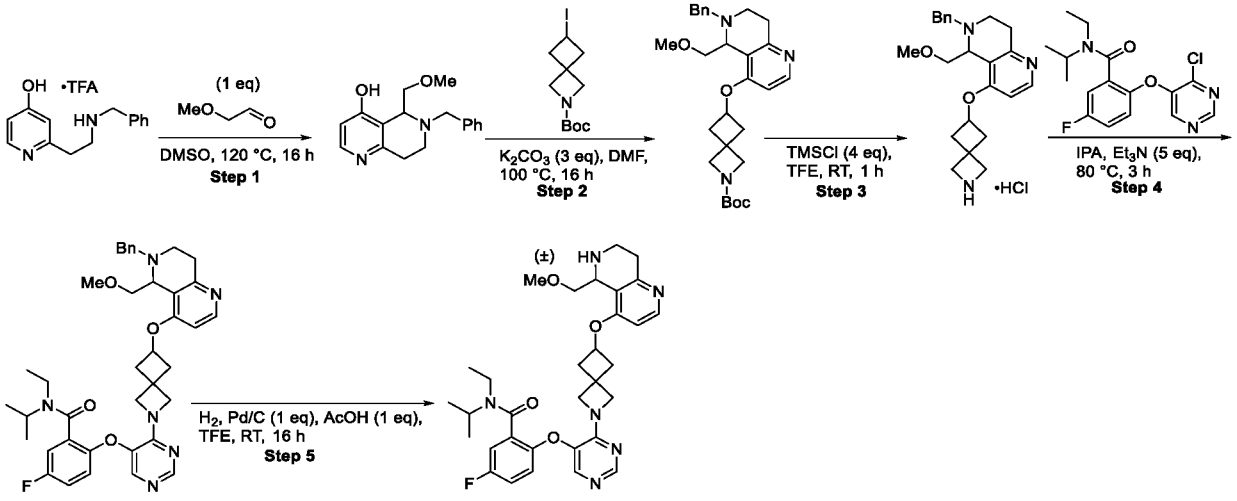
Step 5. (±)-N-Ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



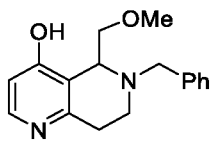
In a 50 mL round bottom flask under an argon atmosphere, (±)-2-((4-(6-((6-benzyl-5-((benzyloxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.2 g, 0.264 mmol) was dissolved in 2,2,2-trifluoroethanol (5 mL). AcOH (7.56 µL, 0.132 mmol) and Pd/C (0.281 g, 0.264 mmol) were added to this solution. The reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The starting material was not consumed. Therefore, another equivalent of Pd-C (0.281 g, 0.264 mmol) was added. The reaction was stirred at RT for an additional 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (3 x 25

mL). The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (36 mg, 23.39% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.19 - 8.14 (m, 1H), 7.78 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.12 - 7.01 (m, 1H), 6.68 - 6.63 (m, 1H), 4.80 - 4.69 (m, 1H), 4.63 (br t, *J* = 5.5 Hz, 1H), 4.46 - 4.08 (m, 4H), 3.95 (dd, *J* = 3.1, 9.0 Hz, 1H), 3.75 (spt, *J* = 6.6 Hz, 1H), 3.61 - 3.54 (m, 1H), 3.49 - 3.37 (m, 2H), 3.29 - 3.13 (m, 1H), 3.12 - 3.04 (m, 1H), 2.92 - 2.85 (m, 1H), 2.83 - 2.69 (m, 3H), 2.66 - 2.54 (m, 1H), 2.30 - 2.20 (m, 2H), 1.23 - 0.98 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.65 min, m/z = 577.3 $[M+H]^+$; HPLC (Method A): Rt = 4.45 min, 98.60%; Chiral SFC (Method J): Peak 1: Rt = 2.84 min, 49.11%; Peak 2: Rt = 4.47 min, 49.47%.

Example 267. (±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 280)



Step 1. (±)-6-Benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol

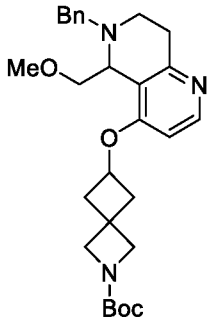


This compound was synthesized following the procedure described for the synthesis of Example 266, step 1, starting with 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 1 equivalent of 2-methoxyacetaldehyde was used. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was

eluted in 17% MeOH in DCM) to afford (±)-6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol 2,2,2-trifluoroacetate as a solid.

Yield: 30.5%; LCMS (Method G): Rt = 1.62 min, m/z = 285.2 $[M+H]^+$; 88.79%.

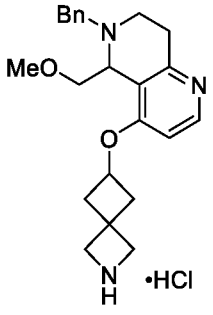
Step 2. (±)-tert-Butyl 6-((6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 1 equivalent of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of 6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 13% MeOH in DCM) to afford (±)-*tert*-butyl 6-((6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a solid.

Yield: 29.2%; LCMS (Method G): Rt = 2.22 min, m/z = 480.4 $[M+H]^+$; 98.34%.

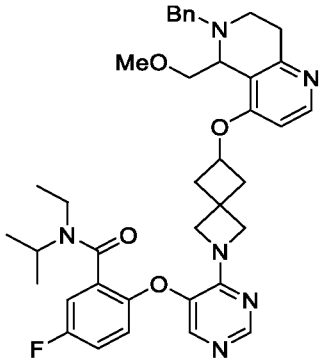
Step 3. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with (±)-*tert*-butyl 6-((6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride. This material was used without further purification.

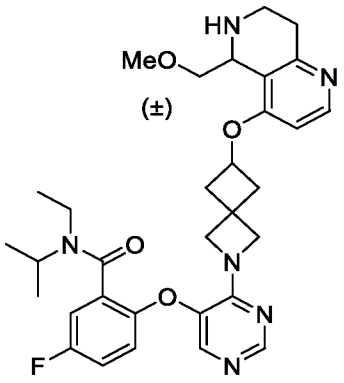
Yield: 89%; LCMS (Method G): Rt = 1.49 min, m/z = 380.4 $[M+H]^+$; 89.24%.

Step 4. (±)-*2-((4-(6-((6-Benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide*



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride was used. After completion, the reaction was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 8% MeOH in DCM) to afford (±)-2-((4-(6-((6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.
Yield: 51.9%; LCMS (Method G): Rt = 2.15 min, m/z = 681.4 $[M+H]^+$; 91.25%.

Step 5. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



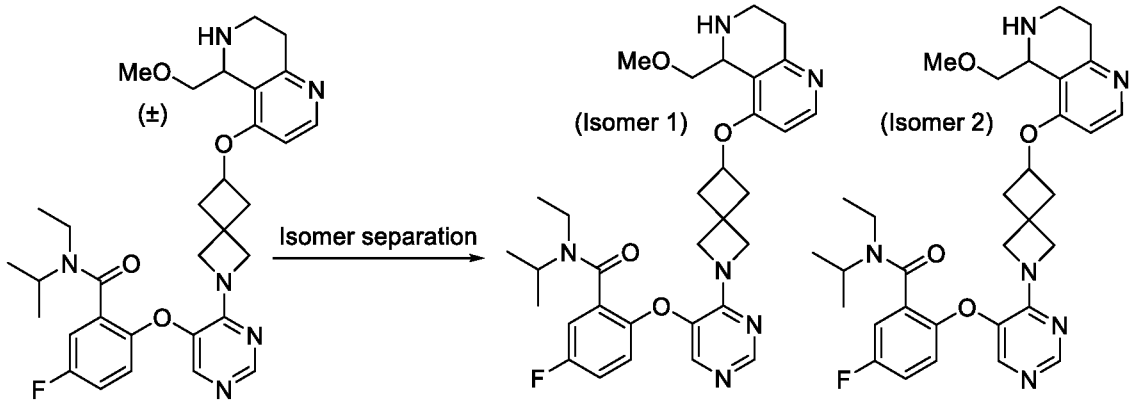
This compound was synthesized following the procedure described for the synthesis of Example 266, step 5, starting with (±)-2-((4-(6-((6-benzyl-5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except 1 equivalent of Pd/C was added at once and 1

equivalent of AcOH was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 54.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.24 (m, 1H), 8.19 (d, J = 5.7 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.67 (d, J = 5.7 Hz, 1H), 4.79 - 4.72 (m, 1H), 4.46 - 4.10 (m, 5H), 3.82 - 3.69 (m, 1H), 3.55 (br t, J = 9.3 Hz, 1H), 3.45 - 3.39 (m, 2H), 3.29 (s, 3H), 3.25 - 3.05 (m, 3H), 2.94 - 2.86 (m, 1H), 2.85 - 2.75 (m, 3H), 2.72 - 2.61 (m, 1H), 2.29 - 2.20 (m, 2H), 1.24 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.69 min, m/z = 591.4 $[M+H]^+$; HPLC (Method A): Rt = 4.78 min, 97.70%. Chiral SFC (Method AH): Peak 1: Rt = 4.83 min, 48.49%; Peak 2: Rt = 6.01 min, 48.42%.

Example 268. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 288)

Example 269. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 289)

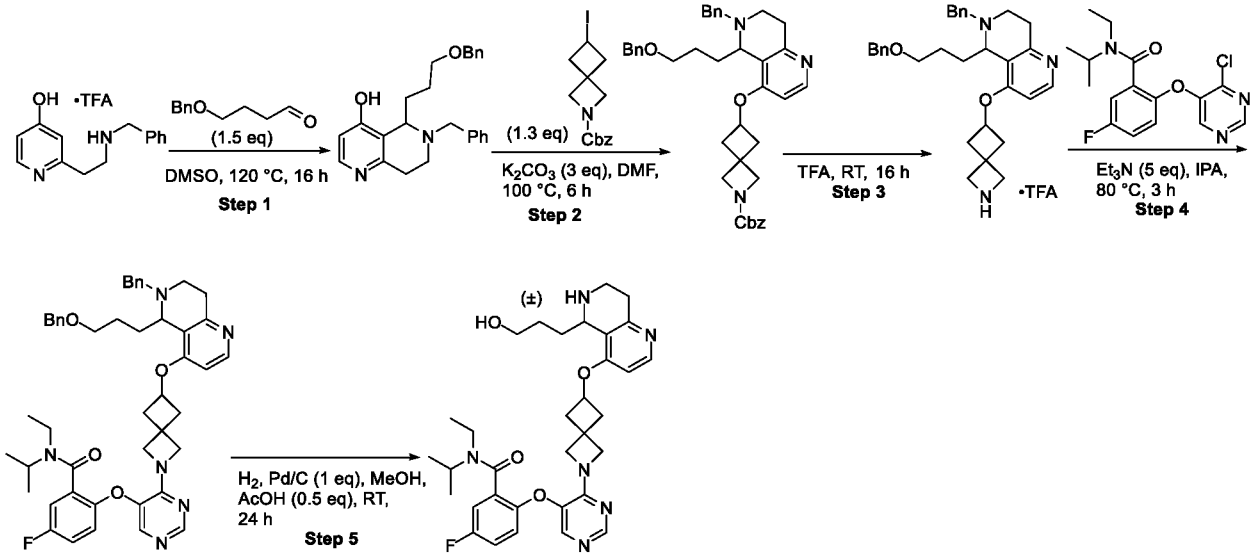


(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (76 mg, 0.129 mmol) was purified by chiral Prep SFC (Method N) to afford (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (18.56 mg, 24.39% yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(methoxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (22.58 mg, 29.7% yield) as solids.

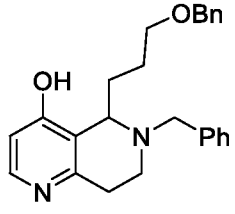
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.21 - 8.17 (m, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.67 (d, J = 5.7 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.47 - 4.09 (m, 5H), 3.81 - 3.69 (m, 1H), 3.55 (t, J =9.3 Hz, 1H), 3.45 - 3.37 (m, 2H), 3.29 (s, 3H), 3.25 - 3.04 (m, 3H), 2.94 - 2.88 (m, 1H), 2.85 - 2.70 (m, 3H), 2.66 - 2.60 (m, 1H), 2.29 - 2.21 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.70 min, m/z = 591.3 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 99.73%; Chiral SFC (Method AH): Rt = 5.18 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.20 - 8.17 (m, 1H), 7.76 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.02 (m, 1H), 6.67 (d, J = 5.7 Hz, 1H), 4.79 - 4.70 (m, 1H), 4.46 - 4.09 (m, 5H), 3.75 (spt, J = 6.6 Hz, 1H), 3.55 (t, J = 9.3 Hz, 1H), 3.44 - 3.37 (m, 2H), 3.29 (s, 3H), 3.27 - 3.06 (m, 3H), 2.95 - 2.85 (m, 1H), 2.84 - 2.69 (m, 3H), 2.66 - 2.59 (m, 1H), 2.30 - 2.16 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.70 min, m/z = 591.3 $[M+H]^+$; 99.92%; HPLC (Method A): Rt = 4.76 min, 99.76%; Chiral SFC (Method AH): Rt = 6.52 min, 100%.

Example 270. (±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 212)



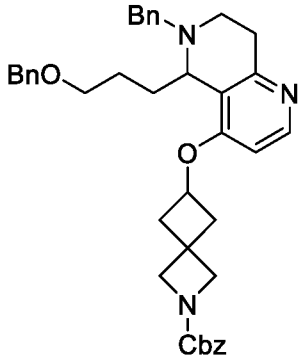
Step 1. (±)-6-Benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



This compound was synthesized following the procedure described for the synthesis of Example 266, step 1, starting with 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 1.5 equivalents of 4-(benzyloxy)butanal was used, and the reaction was stirred in a pressure vial. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 15% MeOH in DCM) to afford (±)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol as a liquid.

Yield: 33.5%; LCMS (Method G): Rt = 1.74 min, m/z = 389.4 $[M+H]^+$; 95.23%.

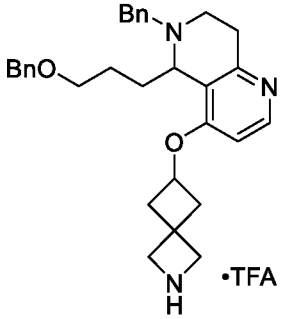
Step 2. (±)-Benzyl 6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 1.3 equivalents of benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent (±)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used, and the reaction was stirred in a pressure vial. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to afford (±)-benzyl 6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a solid.

Yield: 22.94%; LCMS (Method G): Rt = 2.48 min, m/z = 618.6 $[M+H]^+$; 76.01%.

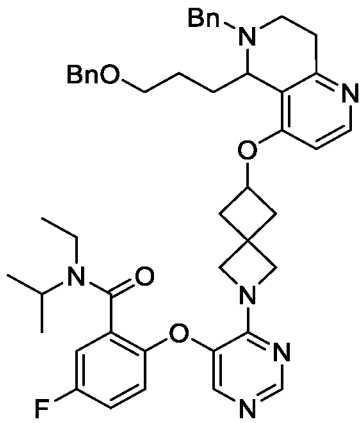
Step 3. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine 2,2,2-trifluoroacetate



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with (±)-benzyl 6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, except that TFA was used as the solvent. After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with MTBE. The organic layer was decanted, and the resulting solid was dried under reduced pressure to obtain (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine 2,2,2-trifluoroacetate as a gum.

Yield: 68.9%; LCMS (Method D): Rt = 1.99 min, m/z = 484.3 $[M+H]^+$; 83.09%.

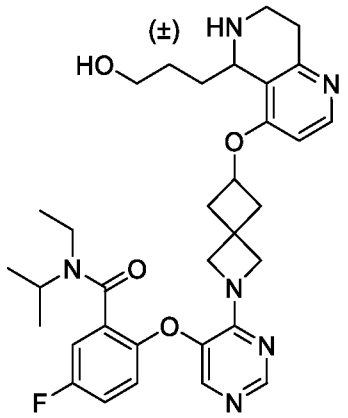
Step 4. (±)-2-((4-(6-((6-Benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine 2,2,2-trifluoroacetate was used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to afford (±)-2-((4-(6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

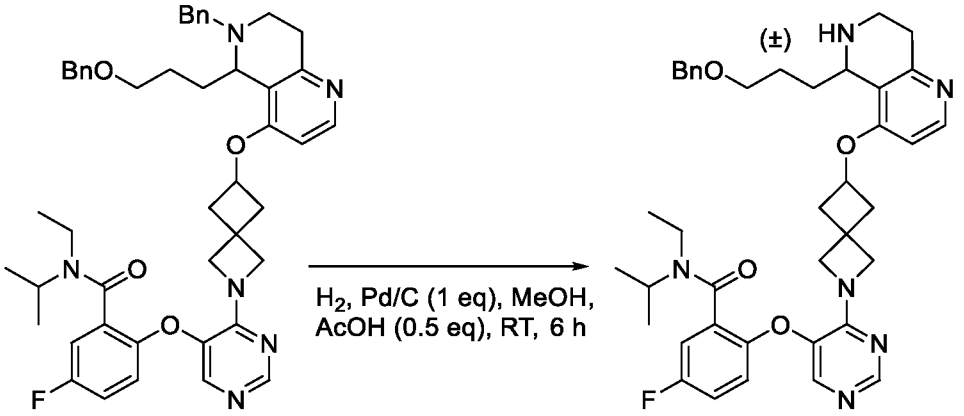
Yield: 53.6%. LCMS (Method D): Rt = 2.48 min, m/z = 785.2 $[M+H]^+$; 89.25%.

Step 5. (±)-N-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 5, starting with (±)-2-((4-(6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent Pd/C was added at once and MeOH was used as a solvent. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 18.36% as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.32 - 7.23 (m, 2H), 7.11 - 7.01 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.77 - 4.69 (m, 2H), 4.42 - 4.07 (m, 4H), 3.84 (br d, J = 7.6 Hz, 1H), 3.81 - 3.69 (m, 1H), 3.47 - 3.37 (m, 3H), 3.26 - 3.12 (m, 2H), 3.07 - 2.86 (m, 2H), 2.84 - 2.74 (m, 2H), 2.65 - 2.59 (m, 2H), 2.30 - 2.15 (m, 2H), 1.67 - 1.50 (m, 4H), 1.24 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.61 min, m/z = 605.4 $[M+H]^+$; HPLC (Method A): Rt = 4.55 min, 99.57%. Chiral SFC (Method AF): Peak 1: Rt = 9.99 min, 49.37%; Peak 2: Rt = 11.17 min, 50.04%.

Example 271. (±)-2-((4-(6-((5-(3-(Benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 215)

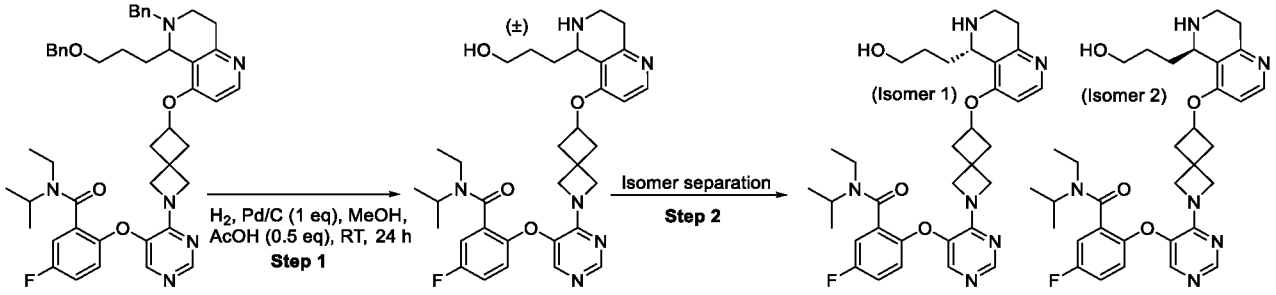


This compound was synthesized following the procedure described for the synthesis of Example 266 step 5, starting with (±)-2-((4-(6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent Pd/C was added at once and MeOH was used as a solvent. The reaction was stirred for 6 h. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were concentrated under reduced pressure to afford (±)-2-((4-(6-((5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

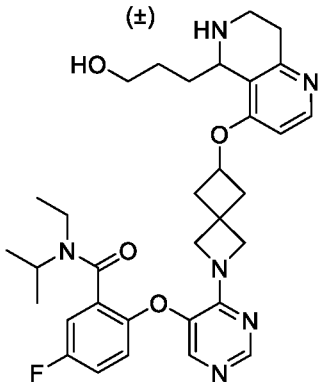
Yield: 27.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.77 - 7.67 (m, 1H), 7.35 - 7.19 (m, 7H), 7.11 - 7.01 (m, 1H), 6.64 - 6.61 (m, 1H), 4.76 - 4.67 (m, 1H), 4.45 (s, 2H), 4.42 - 4.03 (m, 4H), 3.87 (br d, J = 9.0 Hz, 1H), 3.74 (spt, J = 6.5 Hz, 1H), 3.47 (br t, J = 6.0 Hz, 2H), 3.43 - 3.38 (m, 1H), 3.26 - 3.08 (m, 2H), 3.05 - 2.95 (m, 1H), 2.94 - 2.85 (m, 1H), 2.78 - 2.57 (m, 4H), 2.27 - 2.05 (m, 2H), 1.80 - 1.52 (m, 4H), 1.24 - 0.95 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 2.01 min, m/z = 695.4 $[M+H]^+$; HPLC (Method A): Rt = 5.78 min, 99.89%. Chiral SFC (Method AF): Peak 1: Rt = 11.67 min, 49.08%; Peak 2: Rt = 13.24 min, 49.11%.

Example 272. (*E1*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 233)

Example 273. (*E2*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (compound No. 234)

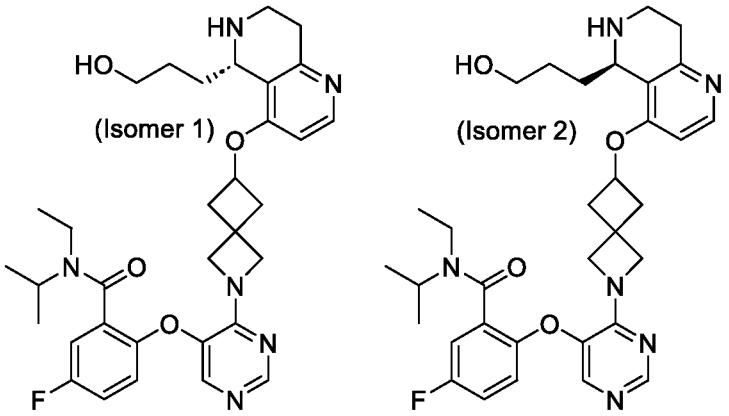


Step 1. (±)-N-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.68 g, 0.866 mmol) in MeOH (7 mL), AcOH (0.025 mL, 0.433 mmol) and Pd/C (0.922 g, 0.866 mmol) were added. The reaction was stirred at RT for 24 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 25 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.62 g, 46.2% yield) as a liquid. LCMS (Method A): Rt = 1.92 min, m/z = 605.3 $[M+H]^+$; 39.77%. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (130 mg, 24.98% yield). LCMS (Method D): Rt = 1.63 min, m/z = 605.4 $[M+H]^+$; 99.92%.

Step 2. *(E1)-N-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide and (E2)-N-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide*



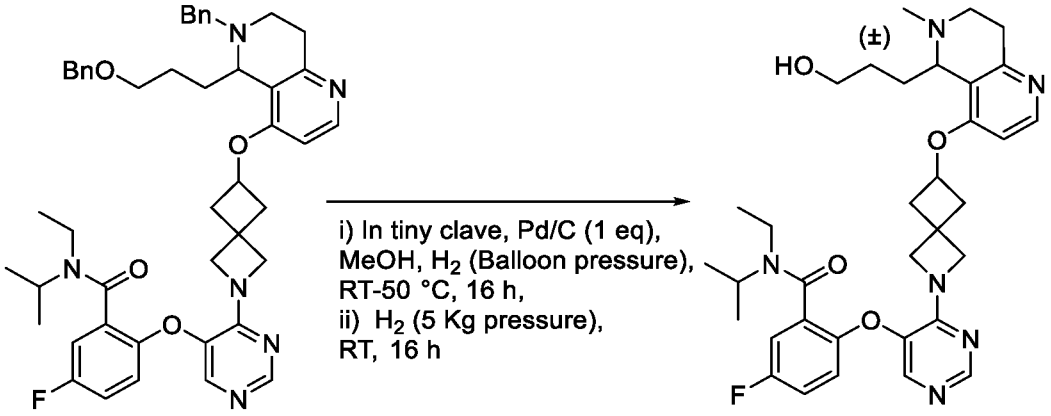
(±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (130 mg, 0.215 mmol) was purified by chiral Prep SFC (Method K). The fractions were concentrated under reduced pressure, re-concentrated from ACN, then lyophilized to obtain (*E1*)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (45 mg, 34.3%) and *(E2)*-*N*-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (35 mg, 26.7%) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.76 - 7.64 (m, 1H), 7.32 - 7.21 (m, 2H), 7.10 - 7.01 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.81 - 4.65 (m, 2H), 4.45 - 4.09 (m, 4H), 3.84 (br d, J = 8.1 Hz, 1H), 3.81 - 3.68 (m, 1H), 3.48 - 3.37 (m, 3H), 3.27 - 3.09 (m, 2H), 3.07 - 2.87 (m, 2H), 2.84 - 2.72 (m, 2H), 2.71 - 2.58 (m, 2H), 2.28 - 2.19 (m, 2H), 1.67 - 1.51 (m, 4H), 1.23 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.63 min, m/z = 605.4 $[M+H]^+$; HPLC (Method A): Rt = 4.45 min, 99.87%; Chiral SFC (Method AH): Rt = 6.77 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.17 - 8.13 (m, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.67 - 6.62 (m, 1H), 4.79 - 4.69 (m, 2H), 4.46 - 4.09 (m, 4H), 3.84 (br d, J = 8.4 Hz, 1H), 3.80 - 3.69 (m, 1H), 3.49 - 3.37 (m, 3H), 3.26 - 3.11 (m, 2H), 3.07 - 2.87 (m, 2H), 2.84 - 2.72 (m, 2H), 2.69 - 2.57 (m, 2H), 2.29 - 2.16 (m, 2H), 1.67 - 1.50 (m, 4H), 1.21 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.65 min,

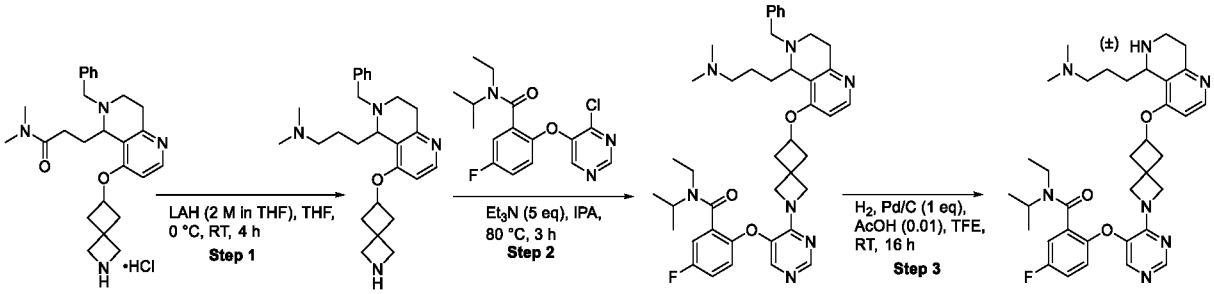
m/z = 605.4 $[M+H]^+$; HPLC (Method A): Rt = 4.47 min, 99.58%; Chiral SFC (Method AH): Rt = 6.88 min, 98.16%.

Example 274. (±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 228)

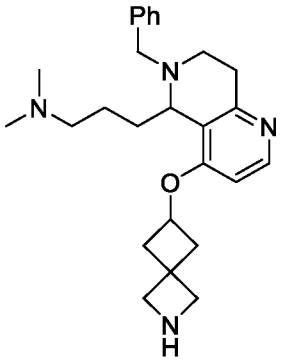


In a tiny clave, to a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (50 mg, 0.064 mmol) in MeOH (5 mL), Pd/C (67.8 mg, 0.064 mmol) was added at RT. The reaction was stirred at 50 °C for 16 h under a hydrogen atmosphere (1 bar pressure). Then, the reaction was cooled to RT, the hydrogen pressure was increased to 5 bar, and the reaction was stirred at RT for another 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (10 mg, 25.1% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 - 8.15 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.69 - 6.64 (m, 1H), 4.79 - 4.70 (m, 1H), 4.52 (br s, 1H), 4.46 - 4.09 (m, 4H), 3.75 (spt, J = 6.6 Hz, 1H), 3.60 - 3.49 (m, 1H), 3.46 - 3.36 (m, 3H), 3.28 - 3.20 (m, 1H), 3.19 - 3.10 (m, 2H), 2.90 - 2.70 (m, 4H), 2.32 (s, 3H), 2.29 - 2.17 (m, 2H), 1.64 - 1.46 (m, 4H), 1.23 - 0.96 (m, 9H); LCMS (Method D): Rt = 1.67 min, m/z = 619.4 $[M+H]^+$; HPLC (Method A): Rt = 4.74 min, 98.70%.

Example 275. (±)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 265)

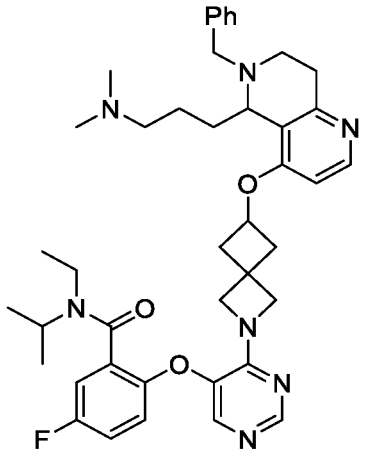


Step 1. (±)-3-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylpropan-1-amine



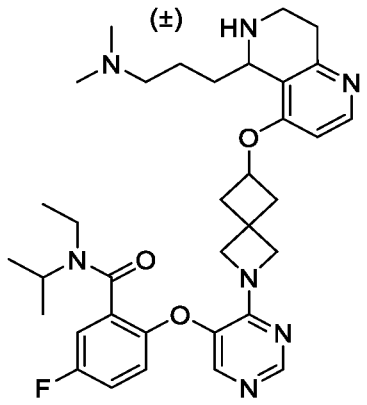
To a stirred solution of (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropanamide hydrochloride (290 mg, 0.616 mmol) in THF (11 mL), lithium aluminum hydride (1.231 mL, 2.463 mmol, 2 M THF) was added dropwise at 0 °C. The reaction was stirred at RT for 4 h. The reaction progress was monitored by TLC (20% MeOH in DCM). The reaction was quenched with ice-cold water (10 mL). The reaction was filtered through a syringe filter and the filtrate was concentrated under reduced pressure to afford crude (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropan-1-amine (200 mg, 37.6% yield) as a solid. LCMS (Method G): Rt = 1.38 min, m/z = 421.4 $[M+H]^+$; 38.41%. This material was used without further purification.

Step 2. (±)-2-((4-(6-((6-Benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



Step 2 was performed following the same procedure in two batches, 23 mg and 148 mg. To a stirred solution of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (148 mg, 0.438 mmol) in IPA (3 mL), TEA (0.305 mL, 2.191 mmol) and (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropan-1-amine (200 mg, 0.438 mmol) were added at RT under nitrogen atmosphere. The reaction was stirred at 80 °C for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction mixtures from both batches were combined for further workup. The reaction was diluted with water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted in 20% MeOH in DCM). The impure product was further purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (35 mg, 8.05% combined yield). LCMS (Method G): Rt = 2.41 min, m/z = 722.4 $[M+H]^+$; 84.11%.

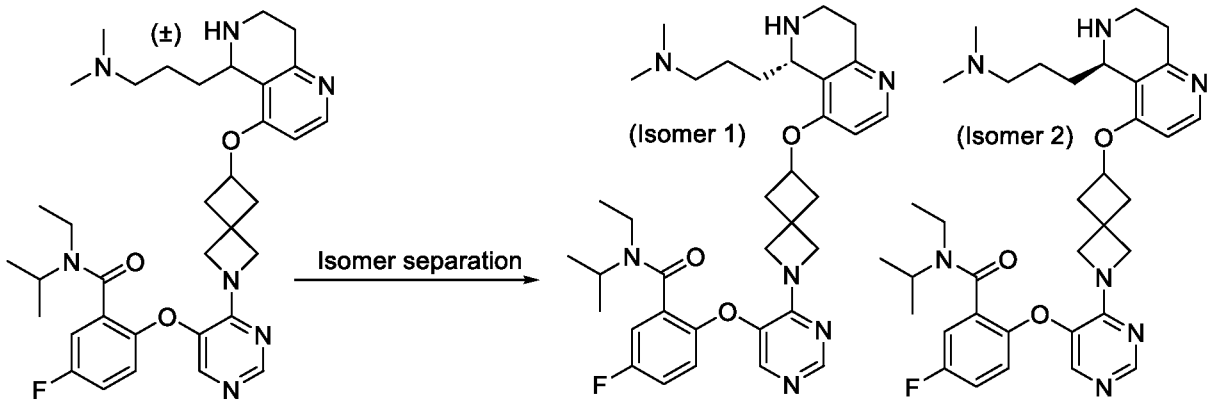
Step 3. (±)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (35 mg, 0.048 mmol) in 2,2,2-trifluoroethanol (2 mL), AcOH (0.029 mg, 0.485 µmol) and Pd-C (51.6 mg, 0.048 mmol) were added at RT. The reaction was stirred for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (6 mg, 18.92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.31 - 8.25 (m, 1H), 8.14 (d, *J* = 5.5 Hz, 1H), 7.76 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.63 (br d, *J* = 5.6 Hz, 1H), 4.79 - 4.71 (m, 1H), 4.45 - 4.07 (m, 4H), 3.88 - 3.81 (m, 1H), 3.79 - 3.69 (m, 1H), 3.43 - 3.40 (m, 1H), 3.26 - 3.11 (m, 2H), 3.05 - 2.74 (m, 4H), 2.66 - 2.62 (m, 1H), 2.28 - 2.15 (m, 4H), 2.10 (s, 6H), 1.64 - 1.47 (m, 4H), 1.22 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.68 min, m/z = 632.3 $[M+H]^+$; HPLC (Method A): Rt = 4.65 min, 97.76%; Chiral SFC (Method J): Peak 1: Rt = 4.19 min, 48.71%; Peak 2: Rt = 5.45 min, 49.70%.

Example 276. (*E1*)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 281)

Example 277. (*E2*)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 282)



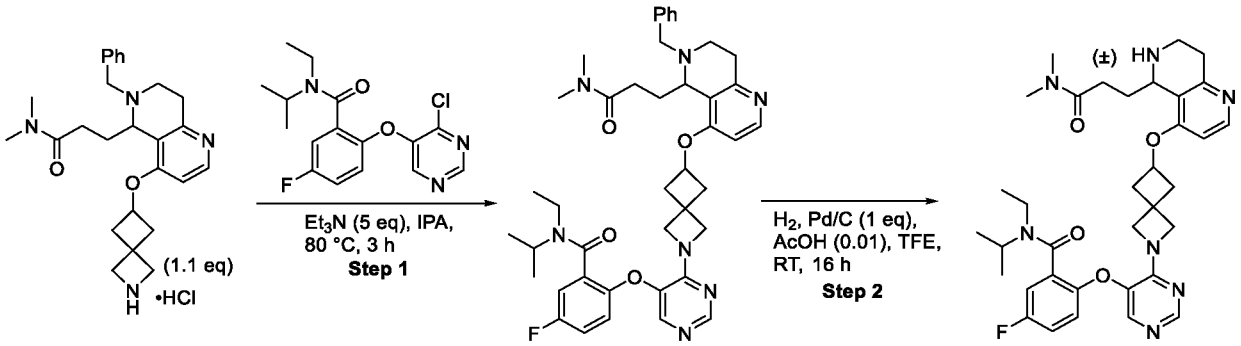
(±)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (106 mg) was purified by chiral Prep SFC (Method M) to obtain both isomers. Due to impurities, both isomers were re-purified individually by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), to obtain both enantiomers. The compounds still contained some impurities by ^{1}HNMR. Therefore, these isomers were each separately diluted with water (5 mL) and extracted with 25% MeOH in DCM (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and lyophilized to afford (*E1*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (16.2 mg, 14.89 % yield) and (*E2*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (11.97 mg, 10.95 % yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.19 (m, 2H), 7.12 - 6.99 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.45 - 4.09 (m, 4H), 3.90 - 3.81 (m, 1H), 3.80 - 3.70 (m, 1H), 3.46 - 3.39 (m, 1H), 3.24 - 3.11 (m, 2H), 3.06 - 2.74 (m, 4H), 2.66 - 2.61 (m, 1H), 2.29 - 2.19 (m, 4H), 2.13 (s, 6H), 1.66 - 1.48 (m, 4H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.71 min, m/z = 632.4 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 98.83%; Chiral SFC (Method AL): Rt = 4.39 min, 97.42%.

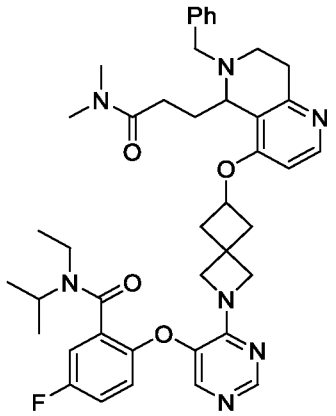
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.63 (br d, J = 5.5 Hz, 1H), 4.78 - 4.69 (m, 1H), 4.44 - 4.08 (m, 4H), 3.88 - 3.83 (m, 1H), 3.79 - 3.69 (m, 1H), 3.44 - 3.37 (m, 1H), 3.27 - 3.12 (m, 2H), 3.05 - 2.79 (m, 4H), 2.65 - 2.61 (m, 1H), 2.28 - 2.15 (m, 4H),

2.10 (s, 6H), 1.64 - 1.48 (m, 4H), 1.22 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.69 min, m/z = 632.4 $[M+H]^+$; 97.00%; HPLC (Method A): Rt = 4.62 min, 97.00%; Chiral SFC (Method AL): Rt = 7.97 min, 98.24%.

Example 278. (±)-2-((4-(6-((5-(3-(Dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 243)



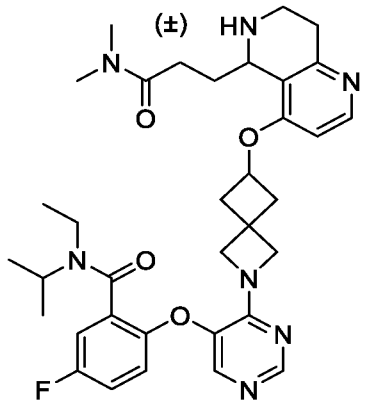
Step 1. (±)-2-((4-(6-((6-Benzyl-5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a stirred solution of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (130 mg, 0.385 mmol) in IPA (3 mL), TEA (0.268 mL, 1.924 mmol) and (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropanamide hydrochloride (199 mg, 0.423 mmol) were added at RT. The reaction was stirred at 80 °C for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7 to 8% MeOH in DCM) to afford (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (300 mg, quantitative) as a solid. LCMS (Method D): Rt = 2.09 min, m/z = 736.4 $[M+H]^+$; 97.24%

Step 2. (±)-2-((4-(6-((5-(3-(Dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



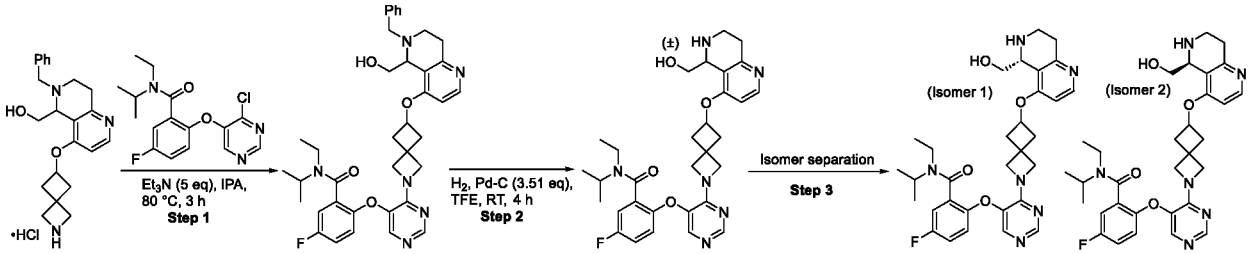
Step 2 was performed following the same procedure in two batches, 30 mg and 270 mg batches.

In a 50 mL round bottom flask under an argon atmosphere, (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (270 mg, 0.367 mmol) was dissolved in 2,2,2-trifluoroethanol (10 mL). AcOH (0.210 µL, 3.67 µmol) and Pd/C (390 mg, 0.367 mmol) were added to this solution. The reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction mixtures from both batches were combined and filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-2-((4-(6-((5-(3-(dimethylamino)-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (77.79 mg, 29.24% combined yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 - 8.13 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.65 (d, J = 5.7 Hz, 1H), 4.78 - 4.69 (m, 1H), 4.46 - 4.08 (m, 4H), 3.86 (br d, J = 10.0 Hz, 1H), 3.75 (spt, J = 6.6 Hz, 1H), 3.44 - 3.36 (m, 1H), 3.27 - 3.11 (m, 2H), 3.02 - 2.87 (m, 5H), 2.82 - 2.74 (m, 5H), 2.66 - 2.61 (m, 1H), 2.47 - 2.40 (m, 2H), 2.28 - 2.19 (m, 2H), 1.92 - 1.66 (m, 2H), 1.22 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method B): Rt =

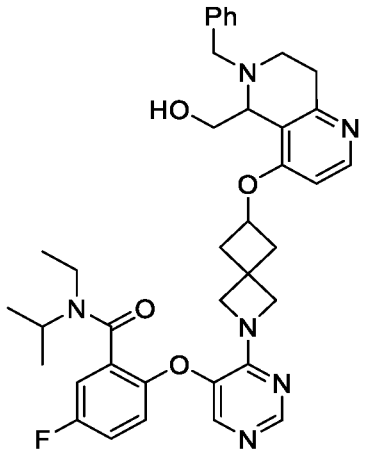
1.11 min, m/z = 646.4 $[M+H]^+$; HPLC (Method A): Rt = 4.56 min, 99.69%; Chiral SFC (Method AM): Peak 1: Rt = 7.35 min, 51.52%; Peak 2: Rt = 10.25 min, 48.48%.

Example 279. (*E1*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 300)

Example 280. (*E2*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 301)



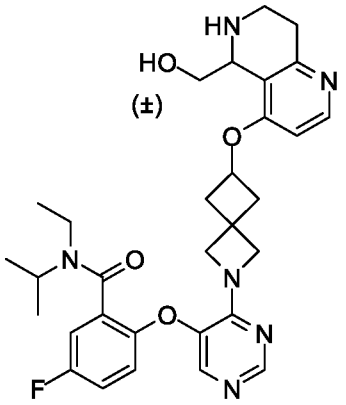
Step 1. (±)-2-((4-(6-((6-Benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanol hydrochloride was used. The crude was purified by silica gel flash column chromatography (100-200 silica) using MeOH in DCM (product was eluted with 7% MeOH in DCM) to afford (±)-2-((4-(6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 51%; LCMS (Method G): Rt = 1.96 min, m/z = 667.3 $[M+H]^+$; 89.97%.

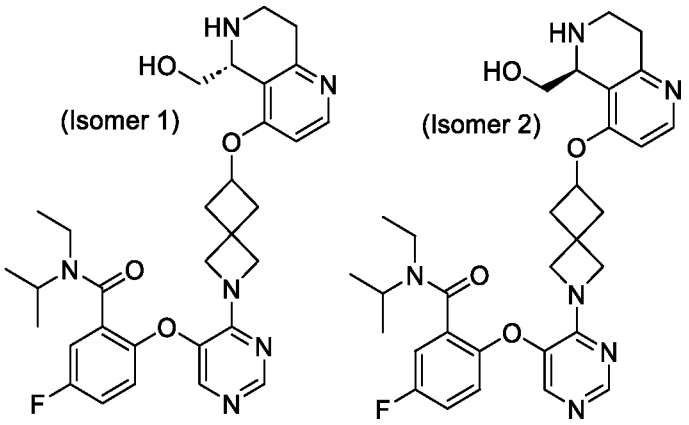
Step 2. (±)-N-Ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.57 g, 0.855 mmol) in TFE (10 mL), Pd/C (0.319 g, 3.00 mmol) was added at RT. The reaction was stirred at RT for 4 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 20 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide ((0.28 g, 56.8% yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.15 (m, 1H), 7.77 - 7.66 (m, 1H), 7.33 - 7.23 (m, 2H), 7.11 - 7.01 (m, 1H), 6.66 (d, J = 5.7 Hz, 1H), 4.78 - 4.69 (m, 1H), 4.65 (br s, 1H), 4.46 - 4.09 (m, 4H), 3.96 (dd, J = 2.9, 8.9 Hz, 1H), 3.75 (spt, J = 6.5 Hz, 1H), 3.60 - 3.55 (m, 1H), 3.49 - 3.37 (m, 2H), 3.28 - 3.12 (m, 1H), 3.11 - 3.05 (m, 1H), 2.93 - 2.85 (m, 1H), 2.85 - 2.70 (m, 3H), 2.67 - 2.60 (m, 1H), 2.29 - 2.20 (m, 2H), 1.25 - 0.98 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.59 min, m/z = 577.4 $[M+H]^+$; HPLC (Method A): Rt = 4.41 min, 96.30%. Chiral SFC (Method J): Peak 1: Rt = 2.96 min, 43.01%; Peak 2: Rt = 4.69 min, 41.16%.

Step 3. (E1)-N-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide and (E2)-N-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-

tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

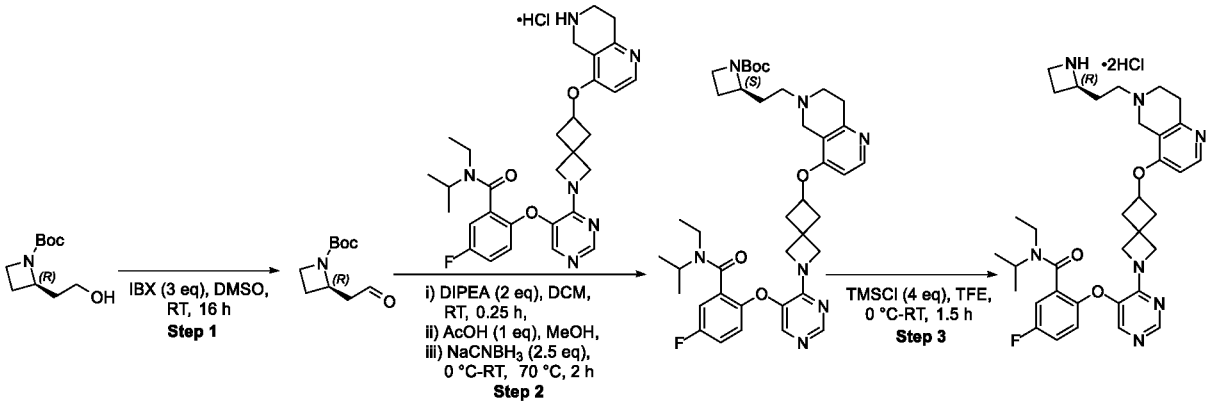


(±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (280 mg, 0.486 mmol) was purified by chiral Prep SFC (Method C) to obtain (*E1*)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.095 g, 33.3% yield) and (*E2*)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.095 g, 33.6% yield) as solids.

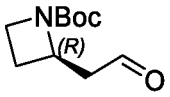
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.19 - 8.16 (m, 1H), 7.76 - 7.64 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.02 (m, 1H), 6.66 (d, J = 5.8 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.46 - 4.10 (m, 4H), 3.96 (dd, J = 3.0, 9.0 Hz, 1H), 3.75 (spt, J = 6.6 Hz, 1H), 3.60 - 3.54 (m, 1H), 3.48 - 3.38 (m, 2H), 3.27 - 3.14 (m, 2H), 3.13 - 3.05 (m, 1H), 2.92 - 2.85 (m, 1H), 2.84 - 2.69 (m, 3H), 2.67 - 2.59 (m, 1H), 2.30 - 2.20 (m, 2H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.55 min, m/z = 577.3 $[M+H]^+$; HPLC (Method A): Rt = 4.39 min, 99.38%; Chiral SFC (Method J): Rt = 3.02 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.20 - 8.15 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 6.99 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.10 (m, 4H), 3.96 (dd, J = 2.9, 8.9 Hz, 1H), 3.81 - 3.70 (m, 1H), 3.58 (br dd, J = 3.1, 10.4 Hz, 1H), 3.48 - 3.40 (m, 2H), 3.26 - 3.18 (m, 2H), 3.13 - 3.04 (m, 1H), 2.94 - 2.70 (m, 4H), 2.67 - 2.59 (m, 1H), 2.29 - 2.17 (m, 2H), 1.21 - 0.97 (m, 9H), one proton merged with solvent peak; LCMS (Method G): Rt = 1.54 min, m/z = 577.3 $[M+H]^+$; 99.04%; HPLC (Method A): Rt = 4.39 min, 99.00%; Chiral SFC (Method J): Rt = 4.93 min, 99.65%.

Example 281. (*R*)-2-((4-(6-((6-(2-(Azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide dihydrochloride (Compound No. 161)

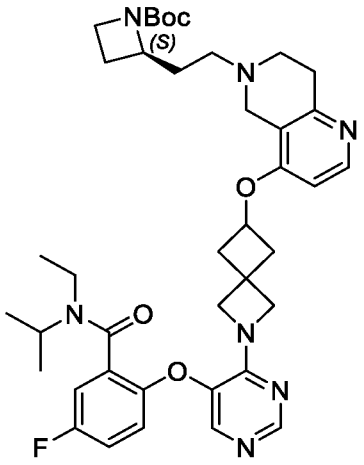


Step 1. tert-Butyl (R)-2-(2-oxoethyl)azetidine-1-carboxylate



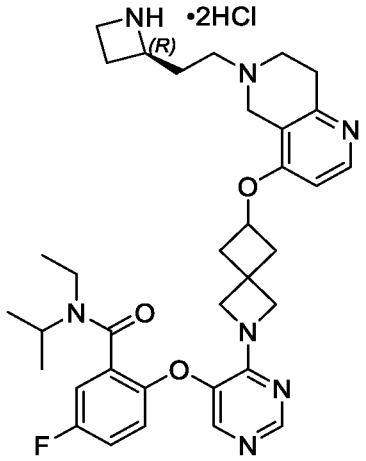
To a stirred solution of IBX (3.25 g, 5.22 mmol) in DMSO (15 mL), *tert*-butyl (*R*)-2-(2-hydroxyethyl)azetidine-1-carboxylate (0.35 g, 1.739 mmol) was added at RT and the reaction was stirred for 16 h. The progress of the reaction was monitored by TLC (40% EtOAc in hexane). After completion, the reaction was cooled to 0 °C, quenched with saturated sodium bicarbonate solution (25 mL), and extracted with MTBE (3 x 25 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (*R*)-2-(2-oxoethyl)azetidine-1-carboxylate (0.35 g) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84-9.82 (m, 1H), 4.70 - 4.59 (m, 1H), 4.00 - 3.80 (m, 2H), 3.08 - 2.95 (m, 1H), 2.87 - 2.72 (m, 1H), 2.50 - 2.23 (m, 1H), 2.02 - 1.87 (m, 1H), 1.46 (s, 9H); This material was used without further purification.

Step 2. tert-Butyl (S)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate



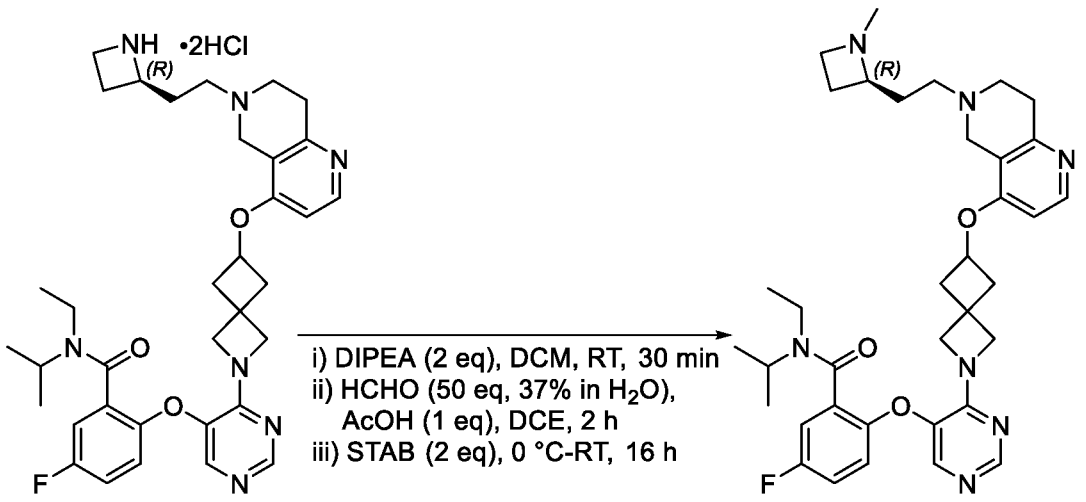
To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.5 g, 0.857 mmol) in DCM (20 mL), DIPEA (0.317 mL, 1.715 mmol) was added at RT. The reaction was stirred at RT for 0.25 h. After completion, the reaction was concentrated under reduced pressure. The crude was dissolved in MeOH (20 mL), and *tert*-butyl (*R*)-2-(2-oxoethyl)azetidine-1-carboxylate (0.256 g, 1.286 mmol) and AcOH (0.049 mL, 0.857 mmol) were added at RT. The reaction was stirred at RT for 2 h, cooled to 0 °C, and $NaCNBH_3$ (0.135 g, 2.144 mmol) was added. The reaction was warmed to RT and stirred at 70 °C for 2 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT, filtered through a Celite® pad, and the pad was washed with DCM (3 x 20 mL). The filtrate was concentrated under reduced pressure. The crude was purified by Prep HPLC (method AL) to obtain *tert*-butyl (*S*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (0.08 g, 12.65% yield) as a solid. LCMS (Method G): Rt = 2.06 min, m/z = 730.5 $[M+H]^+$, 99.96%.

Step 3. (R)-2-((4-(6-((6-(2-(Azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide dihydrochloride



To a stirred solution of *tert*-butyl (*S*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (0.077 g, 0.105 mmol) in 2,2,2-trifluororethanol (4 mL), TMSCl (0.054 mL, 0.422 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was triturated with EtOAc (3 x 5 mL), and the supernatant was decanted. The residue was dried under reduced pressure to obtain crude (*R*)-2-((4-(6-((6-(2-(azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide dihydrochloride (0.07 g, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6, D_2O exchange): δ 8.52 (d, J = 6.3 Hz, 1H), 8.49 - 8.45 (m, 1H), 7.82 - 7.68 (m, 1H), 7.36 - 7.23 (m, 2H), 7.15 (d, J = 6.5 Hz, 1H), 5.03 - 4.93 (m, 1H), 4.51 - 4.28 (m, 4H), 4.23 - 4.16 (m, 2H), 3.83 - 3.62 (m, 4H), 3.51 - 3.41 (m, 2H), 3.41 - 3.32 (m, 1H), 3.28 - 3.07 (m, 6H), 2.93 - 2.82 (m, 2H), 2.45 - 2.35 (m, 4H), 2.31 - 2.19 (m, 2H), 1.24 - 0.90 (m, 9H); LCMS (Method G): Rt = 1.67 min, m/z = 630.3 $[M+H]^+$; HPLC (Method A): Rt = 5.30 min, 98.88%; Chiral SFC (Method T): Rt = 0.98 min, 100%.

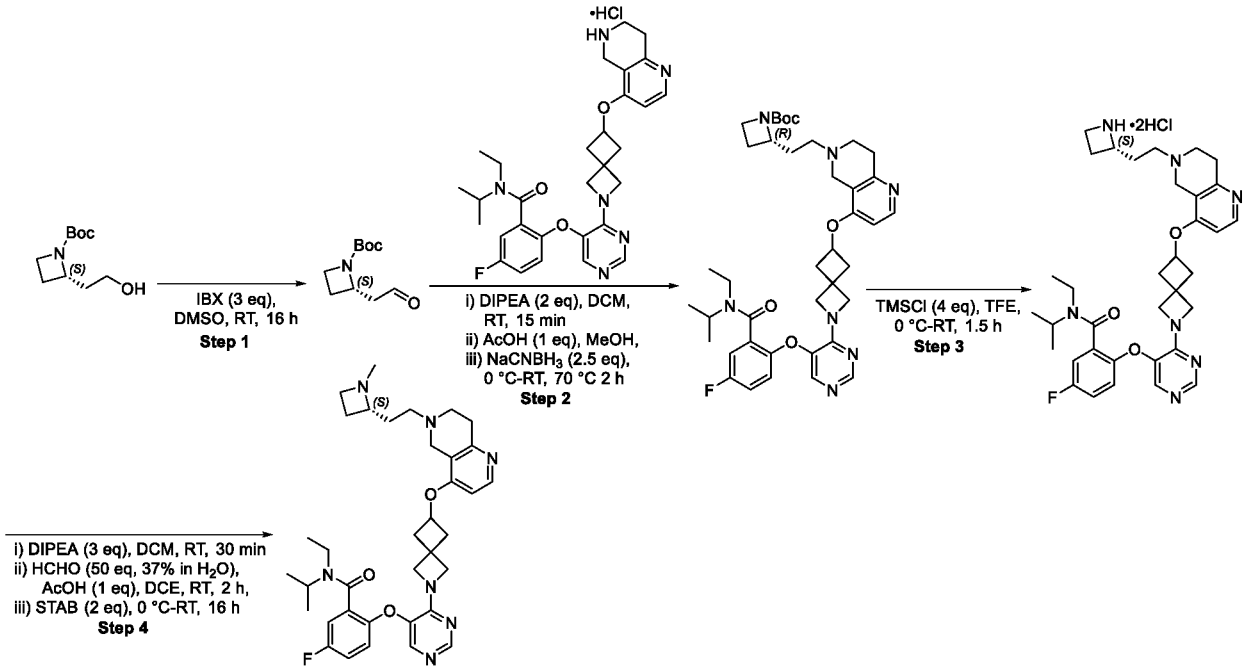
Example 282. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 166)



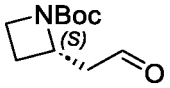
This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*R*)-2-((4-(6-((6-(2-(azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide dihydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 2 equivalents of DIPEA and 2 equivalents of STAB were used. DCE was used as a solvent. The reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 61.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.19 - 8.14 (m, 1H), 7.79 - 7.64 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 - 6.96 (m, 1H), 6.68 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.48 - 3.99 (m, 4H), 3.78-3.75 (m, 1H), 3.50 - 3.36 (m, 3H), 3.28 - 3.11 (m, 1H), 2.96 (br s, 1H), 2.83 - 2.74 (m, 4H), 2.71 - 2.61 (m, 3H), 2.49 - 2.41 (m, 2H), 2.36 - 2.22 (m, 3H), 2.20 (s, 3H), 2.00 - 1.91 (m, 1H), 1.83 - 1.56 (m, 3H), 1.23 - 0.89 (m, 9H); LCMS (Method F): Rt = 1.75 min, m/z = 644.3 $[M+H]^+$; HPLC (Method A): Rt = 4.98 min, 98.77%, Chiral SFC (Method U): Rt = 9.42 min, 100%.

Example 283. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 186)



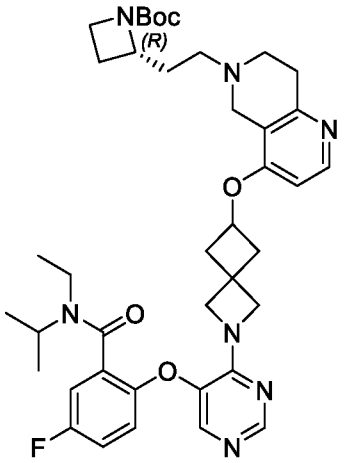
Step 1. tert-Butyl (S)-2-(2-oxoethyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 281, step 1, starting with (*S*)-2-(2-hydroxyethyl)azetidine-1-carboxylate. After completion, the filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (*S*)-2-(2-oxoethyl)azetidine-1-carboxylate as an oil. This material was used without further purification.

Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84-9.83 (m, 1H), 4.67 - 4.60 (m, 1H), 3.95 - 3.77 (m, 2H), 3.09 - 2.97 (m, 1H), 2.83 - 2.72 (m, 1H), 2.49 - 2.39 (m, 1H), 2.01 - 1.89 (m, 1H), 1.46 (s, 9H).

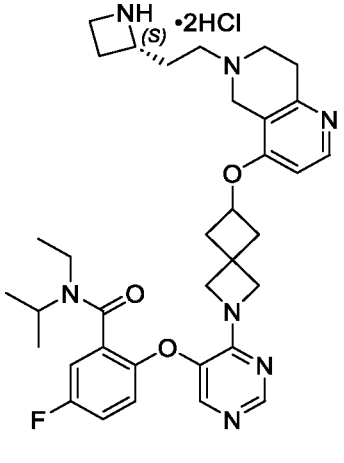
Step 2. tert-Butyl (R)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 281, step 2, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1 equivalent of *tert*-butyl (*S*)-2-(2-oxoethyl)azetidine-1-carboxylate was used. The crude product was purified by Prep HPLC (method AL) to obtain *tert*-butyl (*R*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate as a solid.

Yield: 13.56%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.22 - 8.13 (m, 1H), 7.78 - 7.66 (m, 1H), 7.33 - 7.20 (m, 2H), 7.10 - 6.98 (m, 1H), 6.69 - 6.64 (m, 1H), 4.80 - 4.69 (m, 1H), 4.48 - 4.08 (m, 5H), 3.85 - 3.63 (m, 3H), 3.54 - 3.33 (m, 3H), 3.29 - 3.08 (m, 1H), 2.87 - 2.73 (m, 4H), 2.73 - 2.64 (m, 2H), 2.64 - 2.53 (m, 1H), 2.46 (s, 1H), 2.32 - 2.18 (m, 3H), 2.14 - 2.00 (m, 1H), 1.93 - 1.70 (m, 2H), 1.45 - 1.32 (s, 9H), 1.14 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.96 min, m/z = 730.7 $[M+H]^+$, 97.40%.

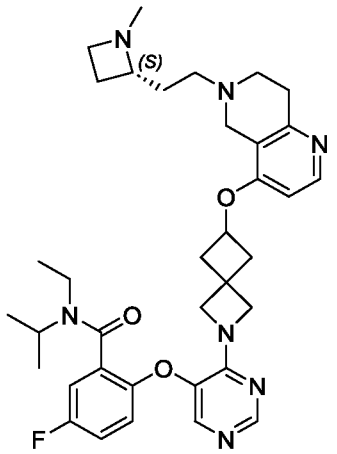
Step 3. (S)-2-((4-(6-((6-(2-(Azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide dihydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 281, step 3, starting with *tert*-butyl (*R*)-2-(2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate. The reaction was concentrated under reduced pressure to obtain crude (*S*)-2-((4-(6-((6-(2-(azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide dihydrochloride. This material was used without further purification.

Yield: 98%; LCMS (Method G): Rt = 1.67 min, m/z = 630.3 $[M+H]^+$; HPLC (Method A): Rt = 5.30 min, 98.88%; Chiral SFC (Method T): Rt = 0.98 min, 100%.

Step 4. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

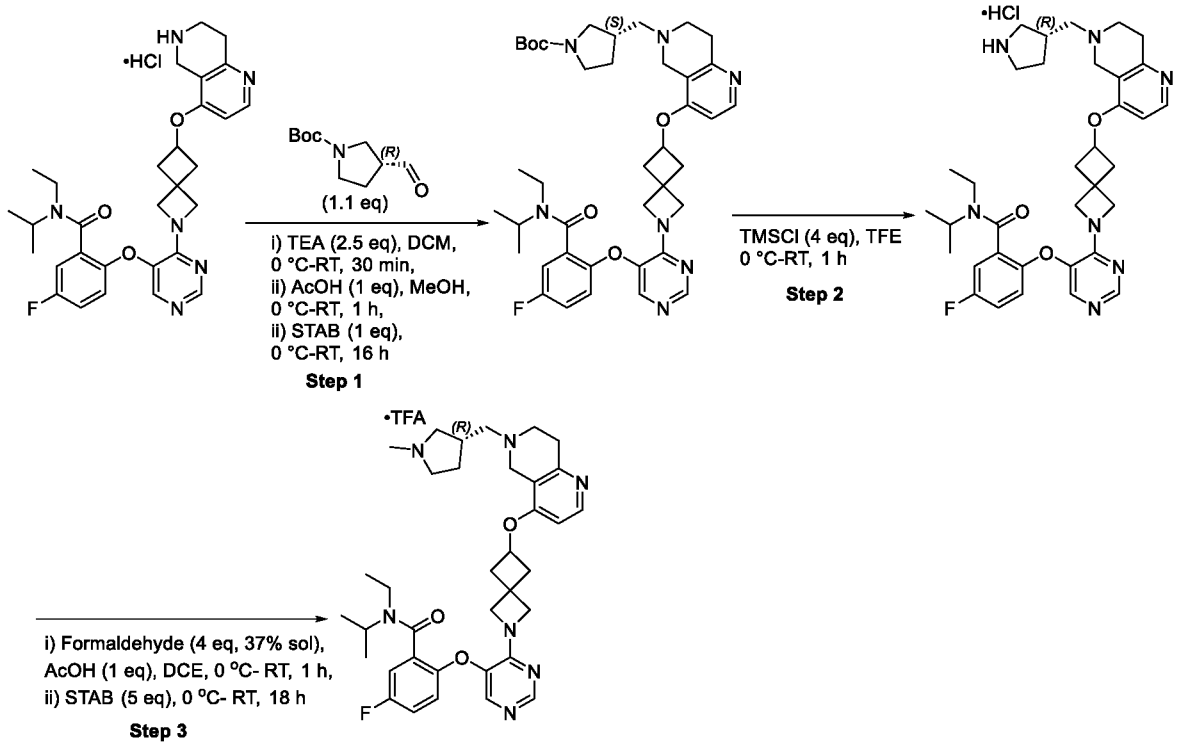


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*S*)-2-((4-(6-((6-(2-(azetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide dihydrochloride and 50 equivalents of formaldehyde (37% in H_2O), except that 2 equivalents of DIPEA and 2 equivalents of STAB were used. DCE was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(1-methylazetidin-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

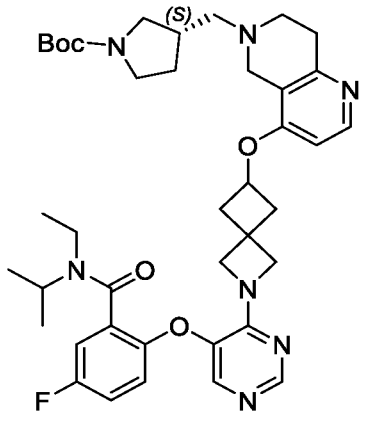
Yield: 61.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.21 - 8.15 (m, 1H), 7.80 - 7.62 (m, 1H), 7.37 - 7.20 (m, 2H), 7.11 - 6.98 (m, 1H), 6.70 - 6.62 (m, 1H), 4.81 - 4.68

(m, 1H), 4.48 - 4.03 (m, 4H), 3.78-3.75 (m, 1H), 3.45 - 3.36 (m, 3H), 3.29 - 3.18 (m, 1H), 2.95-2.92 (m, 1H), 2.84 - 2.72 (m, 5H), 2.70 - 2.56 (m, 3H), 2.48 - 2.42 (m, 2H), 2.32 - 2.21 (m, 2H), 2.18 (s, 3H), 2.01 - 1.87 (m, 1H), 1.81 - 1.55 (m, 3H), 1.23 - 0.90 (m, 9H); LCMS (Method D): Rt = 1.79 min, m/z = 644.4 $[M+H]^+$; HPLC (Method A): Rt = 4.61 min, 97.05%, Chiral SFC (Method U): Rt = 8.53 min, 100%.

Example 284. (*R*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate (Compound No. 86-a)

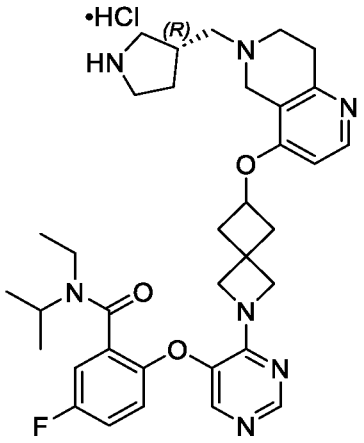


Step 1. tert-Butyl (S)-3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate



In a dried, 50 mL two-neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.2 g, 0.343 mmol) in DCM (3 mL), TEA (0.087 g, 0.857 mmol) was added at 0 °C. The reaction was stirred for at RT 30 min. The reaction was concentrated under reduced pressure. MeOH (5 mL) was added to this reaction mixture, and *tert*-butyl (*R*)-3-formylpyrrolidine-1-carboxylate (0.075 g, 0.377 mmol) and AcOH (0.021 g, 0.343 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (0.073 g, 0.343 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, ice water (50 mL) was added to the residue, and the mixture was extracted with DCM (2 x 100 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 2-5% MeOH in DCM) to obtain *tert*-butyl (*S*)-3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate (0.130 g, 51.9% yield) as a solid. This material was used without further purification.

Step 2. (R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride

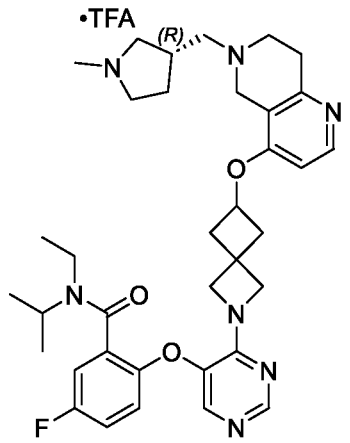


This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl (*S*)-3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate, except that 4 equivalent of TMSCl

was used. After completion, the reaction was concentrated under reduced pressure. The crude was triturated with ethyl acetate, and the supernatant was decanted. The solid was dried under reduced pressure to afford crude (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride as a solid. This material was used without further purification.

Yield: 54.8%; LCMS (Method G): Rt = 1.60 min, m/z = 630.6 $[M+H]^+$; 65.06%.

Step 3. (R)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetic acid

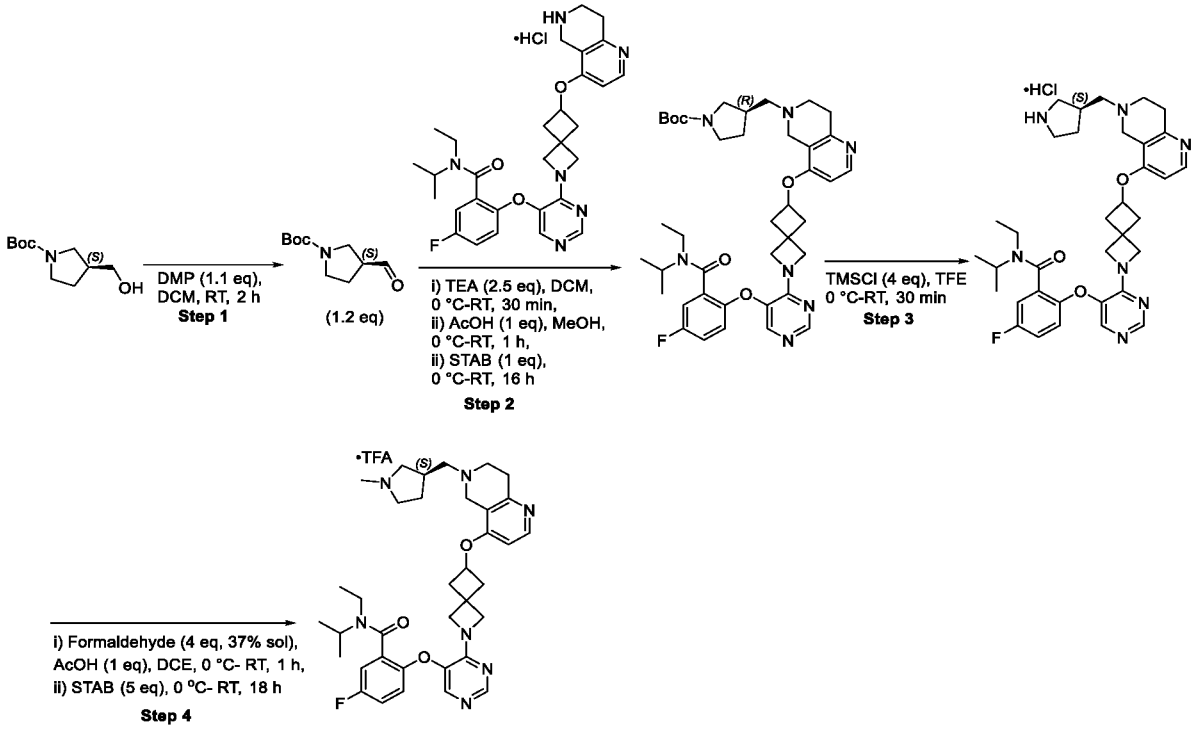


This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 4 equivalent of formaldehyde (37% in H_2O) and 5 equivalents of STAB were used. After completion, the reaction was diluted with water and extracted with DCM. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method X). The product was obtained as a TFA salt. The material was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetic acid as a solid.

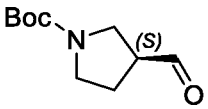
Yield: 7.79%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.78 - 7.68 (m, 1H), 7.33 - 7.22 (m, 2H), 7.09 - 6.99 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H),

4.81 - 4.69 (m, 1H), 4.45 - 4.07 (m, 4H), 3.82 - 3.71 (m, 1H), 3.45 (br s, 2H), 3.42 - 3.35 (m, 1H), 3.25 - 3.11 (m, 2H), 2.85 - 2.71 (m, 7H), 2.66 - 2.60 (m, 1H), 2.43 - 2.36 (m, 2H), 2.30 - 2.20 (m, 3H), 2.05 - 1.93 (m, 1H), 1.57 - 1.46 (m, 1H), 1.23 - 0.98 (m, 9H), four protons merged with solvent peaks; ^{19}F NMR (377 MHz, DMSO-d_6): δ -73.40 (s, 3F), -118.26 (s, 1F); LCMS (Method B): Rt = 1.42 min, m/z = 644.3 $[M+H]^+$; HPLC (Method E): Rt = 2.74 min, 99.54%; SFC (Method J): Rt = 4.48 min, 100%.

Example 285. (*S*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate (Compound No. 118-a)



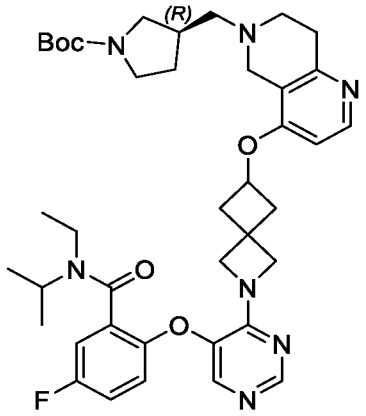
Step 1. tert-Butyl (S)-3-formylpyrrolidine-1-carboxylate



In a dried, 50 mL two-neck round bottom flask under a nitrogen atmosphere, *tert*-butyl (*S*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (1.5 g, 7.45 mmol) was added in DCM (20 mL), and the solution was cooled to 0 °C. Dess-Martin periodinane (3.48 g, 8.20 mmol) was added in one portion at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was diluted with DCM (50 mL) and washed sequentially with saturated $NaHCO_3$ solution (20 mL), then saturated sodium thiosulfate solution (20 mL), then water (20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced

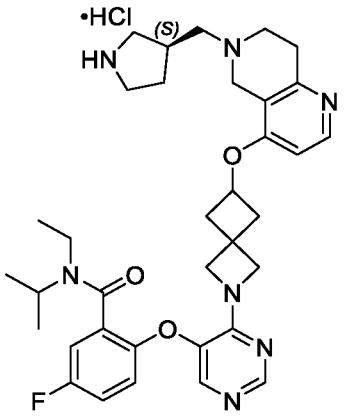
pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 70% EtOAc in hexane). The fractions were concentrated under reduced pressure to obtain *tert*-butyl (*S*)-3-formylpyrrolidine-1-carboxylate (1.1 g, 74.1% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 9.71 (d, J = 1.6 Hz, 1H), 3.79 - 3.32 (m, 4H), 3.04 (br s, 1H), 2.29 - 2.06 (m, 2H), 1.48 (s, 9H).

Step 2. tert-Butyl (R)-3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate



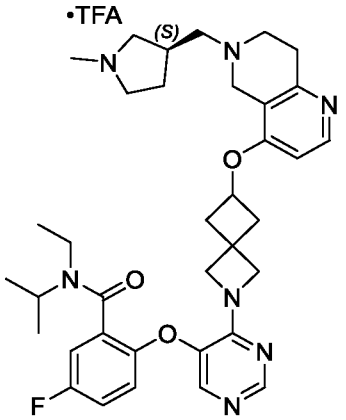
In a dried, 50 mL two neck round bottom flask under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.5 g, 0.857 mmol) was dissolved in DCM (3 mL), and TEA (0.299 mL, 2.144 mmol) was added at 0 °C. The reaction was stirred at RT for 30 min, then was concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL), then *tert*-butyl (*S*)-3-formylpyrrolidine-1-carboxylate (0.205 g, 1.029 mmol) and AcOH (0.051 g, 0.857 mmol) were added at 0 °C. The reaction was stirred for 1 h. To this reaction mixture, sodium triacetoxyborohydride (0.182 g, 0.857 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, ice water (20 mL) was added to the residue, and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 4% MeOH in DCM) to obtain *tert*-butyl (*R*)-3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate (0.450 g, 40.6% yield) as a solid. LCMS (Method B): Rt = 1.79 min, m/z = 730.1 $[M+H]^+$; 56.50%.

Step 3. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl (*R*)-3-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate, except that 4 equivalents of TMSCl was used. The reaction was concentrated under reduced pressure to obtain crude (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride as a solid. This material was used without further purification.
Yield: 58.8%; LCMS (Method G): Rt = 1.73 min, m/z = 630.3 $[M+H]^+$; 66.82%.

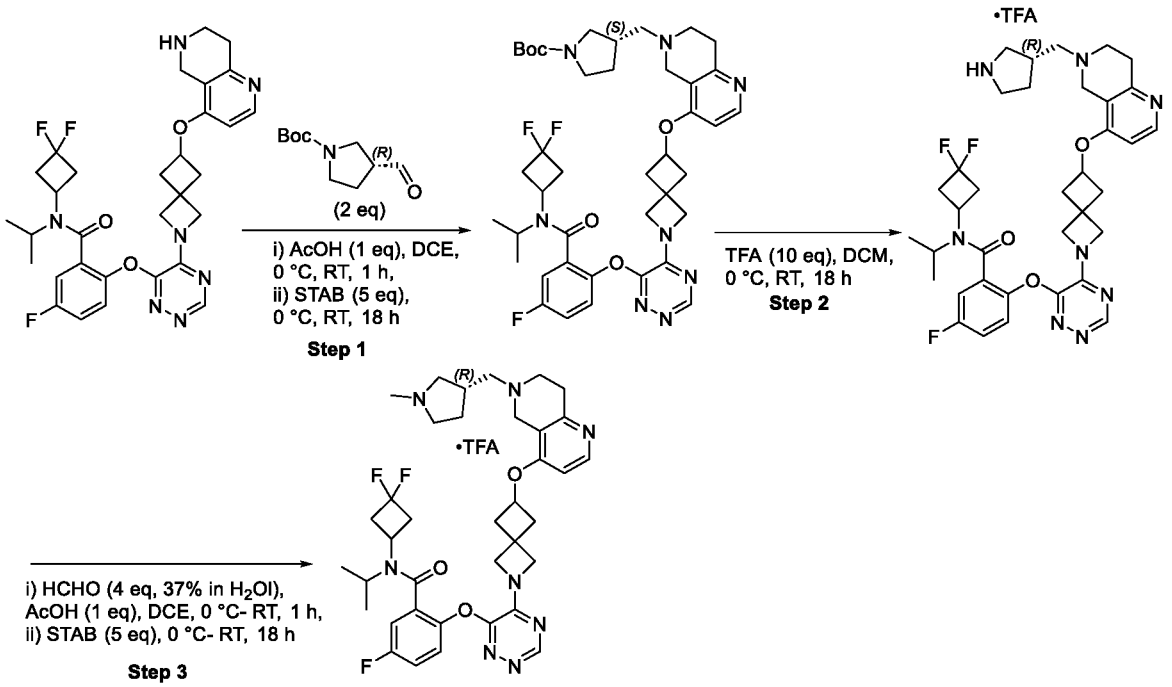
Step 4. (S)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetic acid



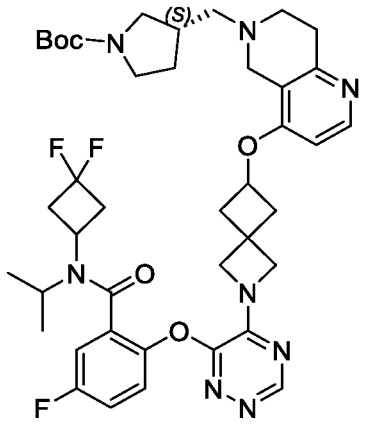
This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-

yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 4 equivalent of formaldehyde (37% in H_2O) and 5 equivalents of STAB were used. The reaction was diluted with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method AA). The product was obtained as a TFA salt. The material was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide 2,2,2-trifluoroacetate as a solid. Yield: 12.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.78 - 7.67 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.79 - 4.69 (m, 1H), 4.43 - 4.07 (m, 4H), 3.81 - 3.70 (m, 1H), 3.47 - 3.37 (m, 3H), 3.27 - 3.09 (m, 2H), 2.83 - 2.70 (m, 6H), 2.67 - 2.60 (m, 2H), 2.46 - 2.35 (m, 4H), 2.29 - 2.21 (m, 2H), 1.98 - 1.88 (m, 1H), 1.52 - 1.43 (m, 1H), 1.21 - 0.98 (m, 9H), three protons merged with solvent peaks; ^{19}F NMR (377 MHz, DMSO-d_6): δ -73.40 (s, 3F), -118.63 (s, 1F); LCMS (Method J): Rt = 1.46 min, m/z = 644.3 $[M+H]^+$; HPLC (Method E): Rt = 2.86 min, 97.73%; SFC (Method J): Rt = 7.57 min, 100%.

Example 286. (*R*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate (Compound No. 278-a)



Step 1. tert-Butyl (S)-3-((4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate

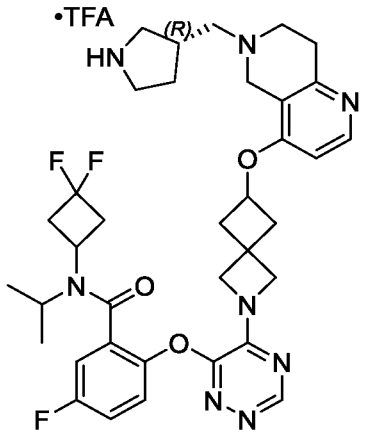


This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1 equivalent of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 2 equivalents of *tert*-butyl (*R*)-3-formylpyrrolidine-1-carboxylate, except that 5 equivalents of STAB and 1 equivalent of AcOH were used, and DCE was used as a solvent. The reaction was quenched with ice water and extracted with 10% MeOH DCM. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain *tert*-butyl (*S*)-3-((4-((2-(6-

(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate as a solid.

Yield: 62.7%; LCMS (Method G): Rt = 2.23 min, m/z = 793.6 $[M+H]^+$; 89.96%.

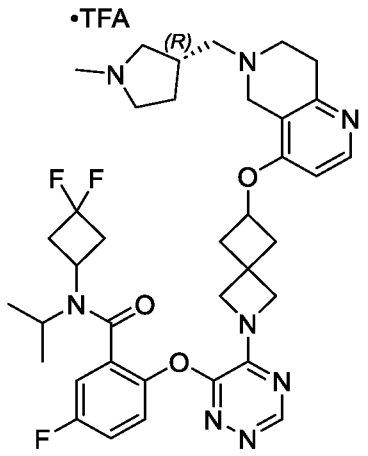
Step 2. (R)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl (*S*)-3-((4-((2-(6-(2-((3,3-difluorocyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)pyrrolidine-1-carboxylate, except that 10 equivalents of TFA was used, and DCM was used as the solvent. After completion, the reaction was quenched with saturated sodium bicarbonate solution at 0 °C and extracted with DCM. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude (*R*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate. This material was used without further purification.

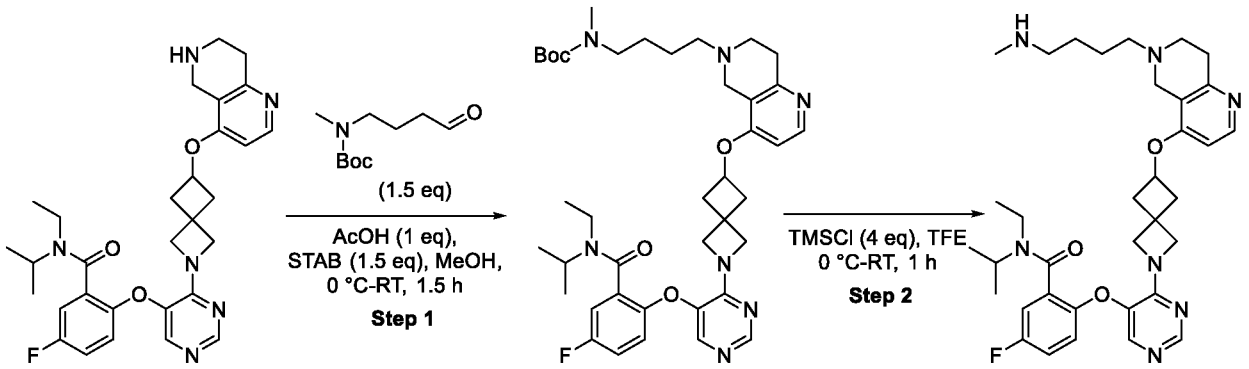
Yield: 78%; ^{19}F NMR (377 MHz, DMSO-d_6): δ -73.41 (s, 3F), -80.96 (d, J = 199.43 Hz, 1F), -96.22 (d, J = 198.30 Hz, 1F), -116.04 (s, 1F); LCMS (Method G): Rt = 1.73 min, m/z = 693.6 $[M+H]^+$; 91.28%.

Step 3. (R)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide

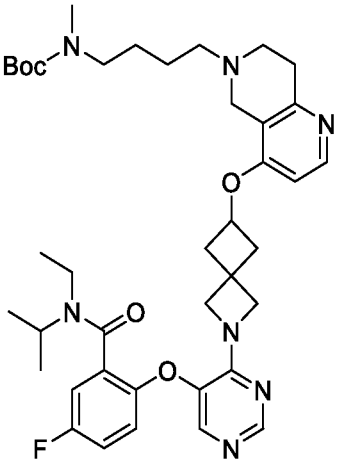


This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with (*R*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(pyrrolidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate, except that 4 equivalents of formaldehyde (37% in H_2O) and 5 equivalents of STAB were used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the product. The obtained product was impure and was re-purified by achiral Prep SFC (Method K) to obtain *(R)-N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylpyrrolidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide 2,2,2-trifluoroacetate (68.09 mg, 11.28% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.50 – 7.35 (m, 3H), 6.67 (br d, J = 3.9 Hz, 1H), 4.79 (quin, J = 6.5 Hz, 1H), 4.68 – 4.50 (m, 2H), 4.30 – 4.13 (m, 2H), 3.85 (br s, 1H), 3.63 (br s, 1H), 3.50 – 3.37 (m, 3H), 2.88 – 2.75 (m, 4H), 2.75 – 2.61 (m, 4H), 2.46 – 2.36 (m, 6H), 2.20 (br s, 3H), 1.94 – 1.79 (br s, 1H), 1.41 (br s, 2H), 1.18 – 0.61 (m, 6H), three protons merged with solvent peaks; ^{19}F NMR (377 MHz, DMSO-d_6): δ -81.01 (d, J = 198.4 Hz, 1F), -96.26 (d, J = 198.30 Hz, 1F), -116.08 (s, 1F); LCMS (Method G): Rt = 1.83 min, m/z = 707.4 $[M+H]^+$; HPLC (Method A): Rt = 5.27 min, 99.79%; Chiral SFC (Method AO): Rt = 1.02 min, 99.16%.

Example 287. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 124)



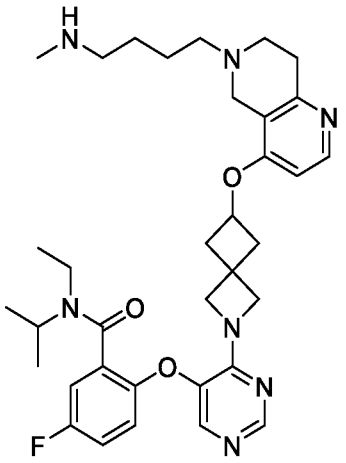
Step 1. tert-Butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)butyl)(methyl)carbamate



In a dried, 25 mL round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (70 mg, 0.128 mmol) was added in methanol (2 mL). To this solution, *tert*-butyl methyl(4-oxobutyl)carbamate (103 mg, 0.512 mmol) and AcOH (7.36 µL, 0.128 mmol) were added, and the reaction was stirred at RT for 30 min. To this reaction mixture, STAB (40.7 mg, 0.192 mmol) was added portion-wise at 0 °C, and the reaction was stirred at RT for 1.5 h. The progress of the reaction was monitored by TLC (7% MeOH in DCM with 3 drops aq. ammonia). After completion, the reaction was concentrated under reduced pressure. The crude was diluted with 10% sodium bicarbonate solution (10 mL) and the mixture was extracted with 10% MeOH in DCM (3 x 10 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 11% MeOH in DCM) to afford *tert*-butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-

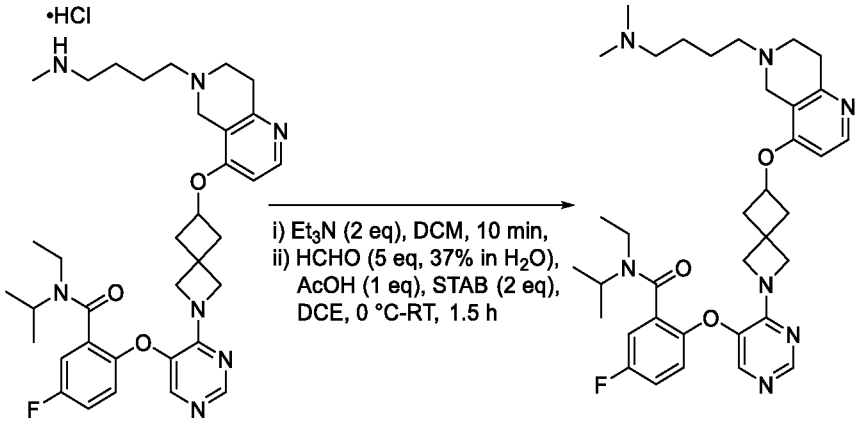
yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)butyl)(methyl)carbamate (87 mg, 50.9% yield) as a viscous liquid. LCMS (Method C): Rt = 2.24 min, m/z = 732.5 $[M+H]^+$, 54.84%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



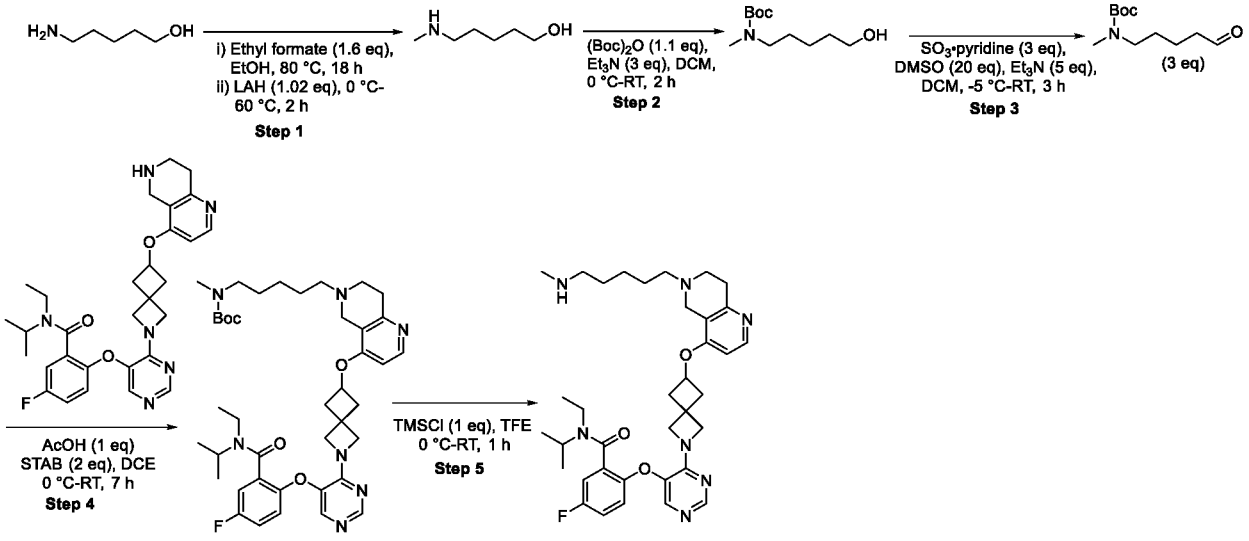
In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)butyl)(methyl)carbamate (85 mg, 0.116 mmol) was added in TFE (2 mL). TMSCl (0.059 mL, 0.465 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. After completion, the reaction was concentrated under reduced pressure to obtain the crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (18 mg, 24.53% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.80 - 7.65 (m, 1H), 7.35 - 7.20 (m, 2H), 7.12 - 6.97 (m, 1H), 6.71 - 6.61 (m, 1H), 4.79 - 4.68 (m, 1H), 4.46 - 4.06 (m, 4H), 3.75 (spt, J = 6.6 Hz, 1H), 3.43 - 3.40 (m, 5H), 3.23 - 3.11 (m, 1H), 2.84 - 2.70 (m, 4H), 2.70 - 2.65 (m, 1H), 2.61 - 2.56 (m, 2H), 2.48 - 2.42 (m, 2H), 2.33 (s, 3H), 2.29 - 2.20 (m, 2H), 1.61 - 1.43 (m, 4H), 1.28 - 0.95 (m, 9H); LCMS (Method A): Rt = 2.11 min, m/z = 632.4 $[M+H]^+$; HPLC (Method A): Rt = 4.62 min, 90.81%.

Example 288. 2-((4-(6-((6-(4-(Dimethylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 104)

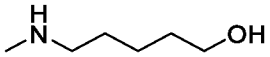


In a dried, 10 mL round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (160 mg, 0.253 mmol) was added in DCM (2 mL). TEA (0.071 mL, 0.506 mmol) was added to this solution, and the reaction was stirred for 10 min. The reaction was concentrated under reduced pressure, and DCE (16 mL) was added to the residue. To this solution, formaldehyde (0.094 mL, 1.266 mmol, 37 wt% in H_2O) and AcOH (0.014 mL, 0.253 mmol) were added, and the reaction was stirred at RT for 30 min. STAB (107 mg, 0.506 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM, 3 drops of aqueous ammonia). After completion, water (25 mL) was added to the reaction and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method B) to obtain 2-((4-(6-((6-(4-(dimethylamino)butyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (61.18 mg, 37.2% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.20 - 8.14 (m, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.62 (m, 1H), 4.80 - 4.69 (m, 1H), 4.45 - 4.08 (m, 4H), 3.75 (spt, J = 6.6 Hz, 1H), 3.45 - 3.36 (m, 3H), 3.28 - 3.12 (m, 1H), 2.84 - 2.74 (m, 4H), 2.69 - 2.64 (m, 2H), 2.48 - 2.44 (m, 2H), 2.30 - 2.17 (m, 4H), 2.10 (s, 6H), 1.55 - 1.36 (m, 4H), 1.22 - 0.96 (m, 9H); LCMS (Method C): Rt = 1.66 min, m/z = 646.4 $[M+H]^+$; HPLC (Method A): Rt = 5.05 min, 99.40%.

Example 289. ***N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(5-(methylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 122)



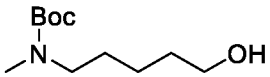
Step1: 5-(Methylamino)pentan-1-ol



This compound was synthesized following the procedure described for the synthesis of Intermediate 46, step 1, starting with 5-aminopentan-1-ol, to obtain crude 5-(methylamino)pentan-1-ol. This material was used without further purification.

Yield: 76%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.41 - 3.35 (m, 4H), 2.45 - 2.38 (m, 2H), 2.25 (s, 3H), 1.47 - 1.37 (m, 6H).

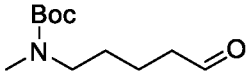
Step 2. tert-Butyl (5-hydroxypentyl)(methyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 46, step 2, starting with 5-(methylamino)pentan-1-ol, to obtain crude *tert*-butyl (5-hydroxypentyl)(methyl)carbamate. This material was used without further purification.

Yield: 58%; LCMS (Method B): Rt = 2.03 min, m/z = 118.2 $[M+H-100]^+$, 16.82%.

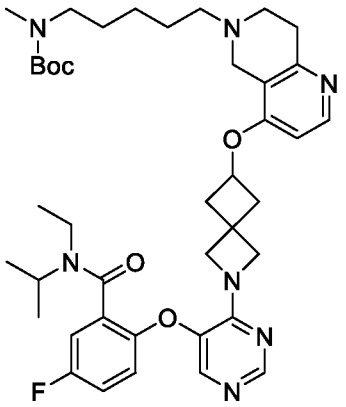
Step 3. tert-Butyl methyl(5-oxopentyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 46, step 3, starting with *tert*-butyl (5-hydroxypentyl)(methyl)carbamate, to obtain crude *tert*-butyl methyl(5-oxopentyl)carbamate. This material was used without further purification.

Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 3.35 - 3.07 (m, 2H), 2.84 (s, 3H), 2.53 - 2.45 (m, 2H), 2.01 - 1.86 (m, 2H), 1.65 - 1.51 (m, 2H), 1.49 - 1.43 (m, 9H).

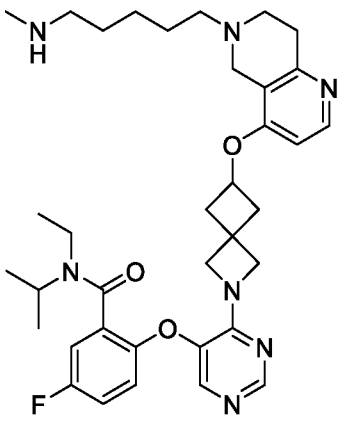
Step 4. tert-Butyl (5-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)pentyl)(methyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Example 287, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 3 equivalents of *tert*-butyl methyl(5-oxopentyl)carbamate and 1.5 equivalents of STAB were used, and DCE was used as a solvent. The crude product was purified by silica gel flash column chromatography using 10% MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain *tert*-butyl (5-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)pentyl)(methyl)carbamate as a solid.

Yield: 55.5%; LCMS (Method G): Rt = 2.18 min, m/z = 746.5 $[M+H]^+$, 94.68%.

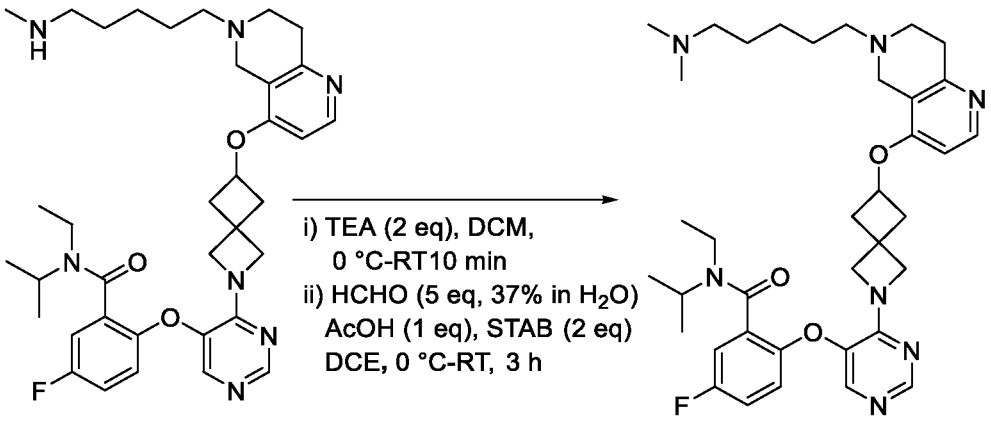
Step 5. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(5-(methylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 287, step 2, starting with *tert*-butyl (5-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)pentyl)(methyl)carbamate, except that 1 equivalent of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to afford crude obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(5-(methylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: CAN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(5-(methylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 19.79%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 – 8.25 (m, 1H), 8.21 – 8.15 (m, 1H), 7.79 – 7.65 (m, 1H), 7.34 – 7.17 (m, 2H), 7.10 – 6.98 (m, 1H), 6.72 – 6.63 (m, 1H), 4.80 – 4.69 (m, 1H), 4.34 – 4.02 (m, 4H), 3.76 (spt, J = 6.6 Hz, 1H), 3.44 – 3.36 (m, 4H), 3.27 – 3.11 (m, 2H), 2.85 – 2.73 (m, 4H), 2.71 – 2.63 (m, 2H), 2.50 – 2.43 (m, 3H), 2.29 (s, 3H), 2.28 – 2.22 (m, 2H), 1.57 – 1.39 (m, 4H), 1.38 – 1.26 (m, 2H), 1.23 – 0.96 (m, 9H); LCMS (Method G): Rt = 1.59 min, m/z = 646.6 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 95.55%.

Example 290. 2-((4-(6-((6-(5-(Dimethylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 114)

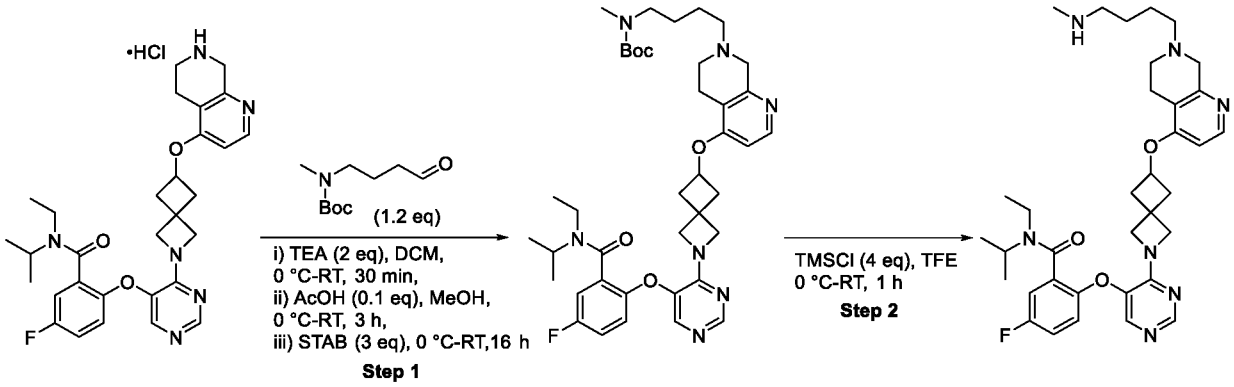


This compound was synthesized following the procedure described for the synthesis of Example 288, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(5-(methylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide. After completion, the reaction was quenched with 10%

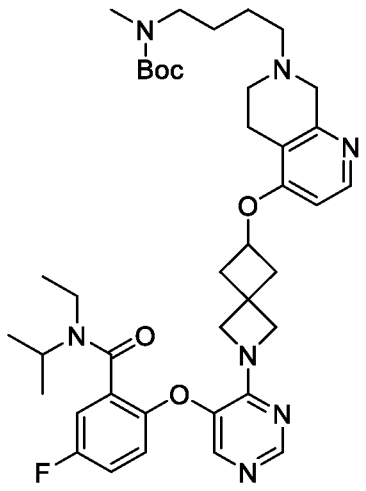
$NaHCO_3$ solution and extracted with 10% MeOH in DCM. The combined organic layers were dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-(5-(dimethylamino)pentyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 36.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.83 - 4.68 (m, 1H), 4.34 - 4.06 (m, 4H), 3.81 - 3.69 (m, 1H), 3.45 - 3.36 (m, 3H), 3.27 - 3.13 (m, 1H), 2.84 - 2.74 (m, 4H), 2.71 - 2.62 (m, 2H), 2.47 - 2.42 (m, 2H), 2.31 - 2.23 (m, 2H), 2.17 (t, J = 7.2 Hz, 2H), 2.10 (s, 6H), 1.56 - 1.47 (m, 2H), 1.46 - 1.37 (m, 2H), 1.35 - 1.25 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.67 min, m/z = 660.6 $[M+H]^+$; HPLC (Method A): Rt = 5.14 min, 99.38%.

Example 291. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 167)

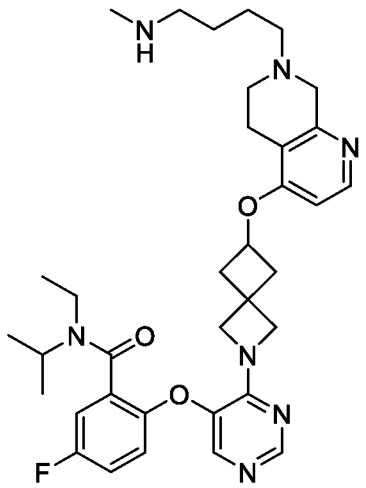


Step 1. tert-Butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)butyl)(methyl)carbamate



In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (200 mg, 0.366 mmol) was added in DCM (5 mL). TEA (0.102 mL, 0.732 mmol) was added to this solution at 0 °C, and the reaction was stirred at the same temperature for 30 min. The reaction was concentrated under reduced pressure. To this residue, MeOH (5 mL), *tert*-butyl methyl(4-oxobutyl)carbamate (88 mg, 0.439 mmol), and AcOH (2.092 µl, 0.037 mmol) were added at 0 °C, and the reaction was stirred at RT for 3 h. Sodium triacetoxyborohydride (233 mg, 1.098 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM) and LCMS. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 4-5% MeOH in DCM) to obtain *tert*-butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)butyl)(methyl)carbamate (100 mg, 33.1% yield) as an oil. LCMS (Method G): Rt = 2.16 min, m/z = 732.5 $[M+H]^+$; 88.73%.

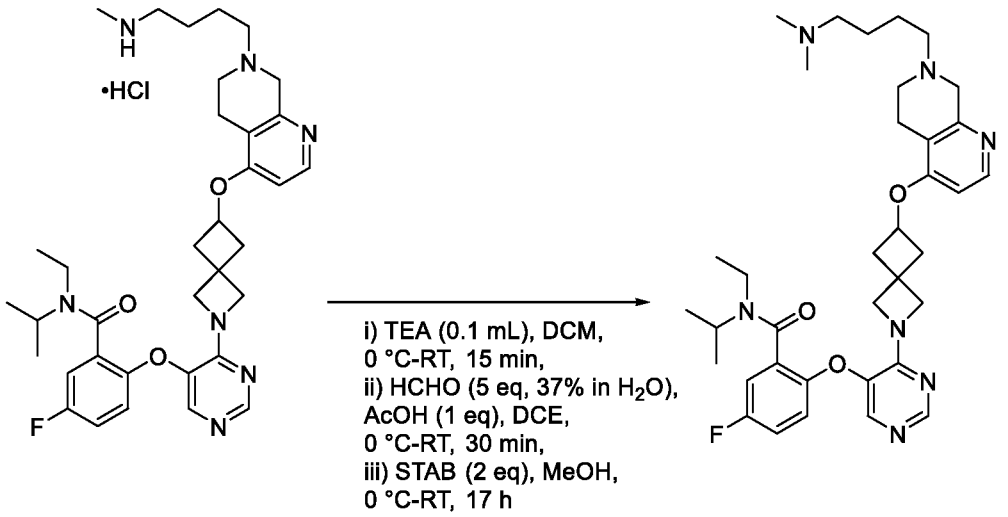
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((7-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 287, step 2, starting with *tert*-butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)butyl)(methyl)carbamate. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 51.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.33 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.81 - 4.68 (m, 1H), 4.46 - 4.07 (m, 4H), 3.81 - 3.70 (m, 1H), 3.47 (s, 2H), 3.43 - 3.37 (m, 1H), 3.27 - 3.12 (m, 2H), 2.84 - 2.75 (m, 2H), 2.60 (br s, 4H), 2.56 - 2.52 (m, 1H), 2.46 - 2.42 (m, 2H), 2.29 - 2.20 (m, 5H), 1.57 - 1.38 (m, 4H), 1.22 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.37 min, m/z = 632.2 $[M+H]^+$; HPLC (Method A): Rt = 4.60 min, 96.08%.

Example 292. 2-((4-(6-((7-(4-(Dimethylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 182)

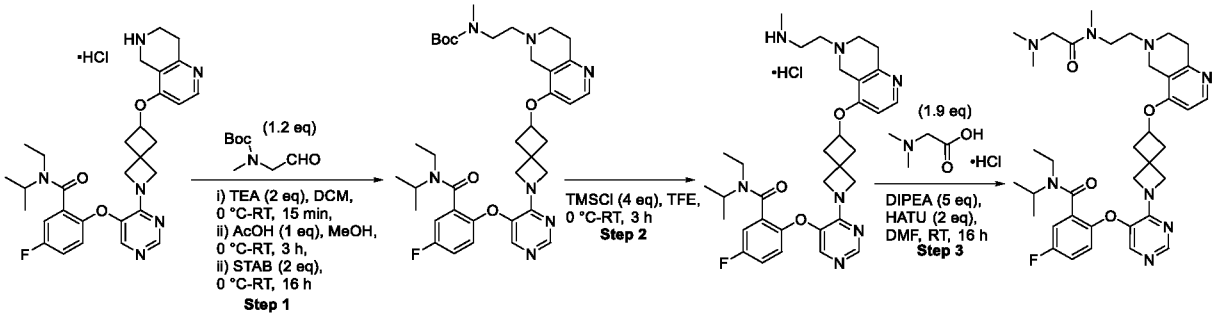


This reaction was performed following the same procedure in two batches, 30 mg and 75 mg batches.

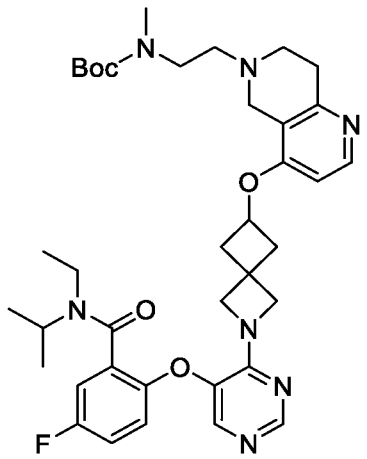
In a dried, 25 mL round bottom flask a under nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((7-(4-(methylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (75 mg, 0.112 mmol) was added in DCM (3 mL). TEA (0.1 mL) was added to this solution, and the reaction was stirred for 15 min. The reaction was concentrated under reduced pressure. DCE (3 mL) was added to this crude, and then formaldehyde (0.042 mL, 0.561 mmol, 37 wt% in H_2O) and AcOH (6.42 µL, 0.112 mmol) were added, respectively, at 0 °C. The reaction was stirred for 30 min at RT. To this reaction mixture, sodium triacetoxyborohydride (47.6 mg, 0.224 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The starting material was not consumed. Therefore, MeOH (3.00 mL) was added to the reaction mixture, and another lot of formaldehyde (0.042 mL, 0.561 mmol, 37 wt% in H_2O) and AcOH (6.42 µL, 0.112 mmol) were added at 0 °C. The reaction was stirred at RT for 30 min. To this mixture, sodium triacetoxyborohydride (47.6 mg, 0.224 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM and 3 drops aq. ammonia). The reaction mixtures from both batches were combined, diluted with 10% $NaHCO_3$ solution (10 mL), and extracted with 10% MeOH in DCM (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method W) to obtain 2-((4-(6-((7-(4-(dimethylamino)butyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (21.36 mg, 21% combined yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.77 - 7.67 (m, 1H), 7.34 - 7.22

(m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.80 - 4.79 (m, 1H), 4.45 - 4.07 (m, 4H), 3.80 - 3.68 (m, 1H), 3.47 (s, 2H), 3.44 - 3.37 (m, 1H), 3.28 - 3.10 (m, 2H), 2.84 - 2.74 (m, 2H), 2.60 (br s, 4H), 2.47 - 2.43 (m, 2H), 2.29 - 2.18 (m, 3H), 2.10 (s, 6H), 1.58 - 1.37 (m, 4H), 1.26 - 0.97 (m, 9H); LCMS (Method D): Rt = 1.75 min, m/z = 646.4 $[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 97.86%.

Example 293. 2-((4-(6-((6-(2-(2-(Dimethylamino)-*N*-methylacetamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 226)



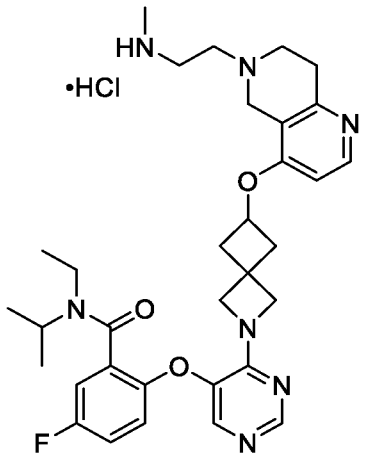
Step 1. tert-Butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)(methyl)carbamate



Step 1 was performed following the same procedure in two batches, 1 g and 0.1 g batches. To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (0.1 g, 0.171 mmol) in DCM (2 mL), Et_3N (0.047 mL, 0.343 mmol) was added at 0 °C. The reaction was stirred at RT for 15 min. The reaction was concentrated under reduced pressure. To this crude material, MeOH (2 mL) was added, then *tert*-butyl methyl(2-oxoethyl)carbamate (0.036 g, 0.206 mmol) and AcOH (9.81 µL, 0.171 mmol) were added at 0 °C. The reaction was stirred at RT for 3 h. To this reaction mixture, sodium

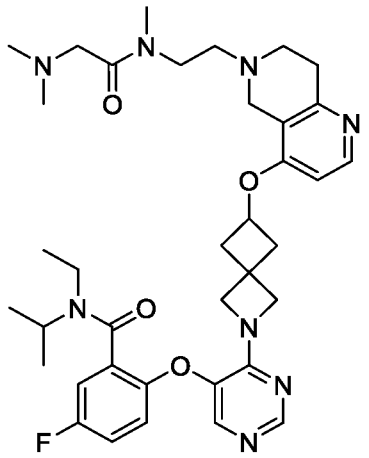
triacetoxyborohydride (0.073 g, 0.343 mmol) was added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction mixtures from both batches were mixed for workup and purification. The reaction was diluted with water (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 3-4% MeOH in DCM) to obtain *tert*-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)(methyl)carbamate (600 mg, 45.18% combined yield).
LCMS (Method G): Rt = 1.92 min, m/z = 704.6 $[M+H]^+$; 87.06%.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *tert*-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)(methyl)carbamate (600 mg, 0.852 mmol) in 2,2,2-trifluoroethanol (6 mL) under a nitrogen atmosphere, TMSCl (0.436 mL, 3.41 mmol) was added at 0 °C. The reaction was stirred at RT for 3 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The residue was re-concentrated from EtOAc (2 x 20 mL) to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (600 mg, 97% yield).
LCMS (Method D): Rt = 1.62 min, m/z = 604.3 $[M+H]^+$; 88.62%. This material was used without further purification.

Step 3. 2-((4-(6-((6-(2-(2-(Dimethylamino)-N-methylacetamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

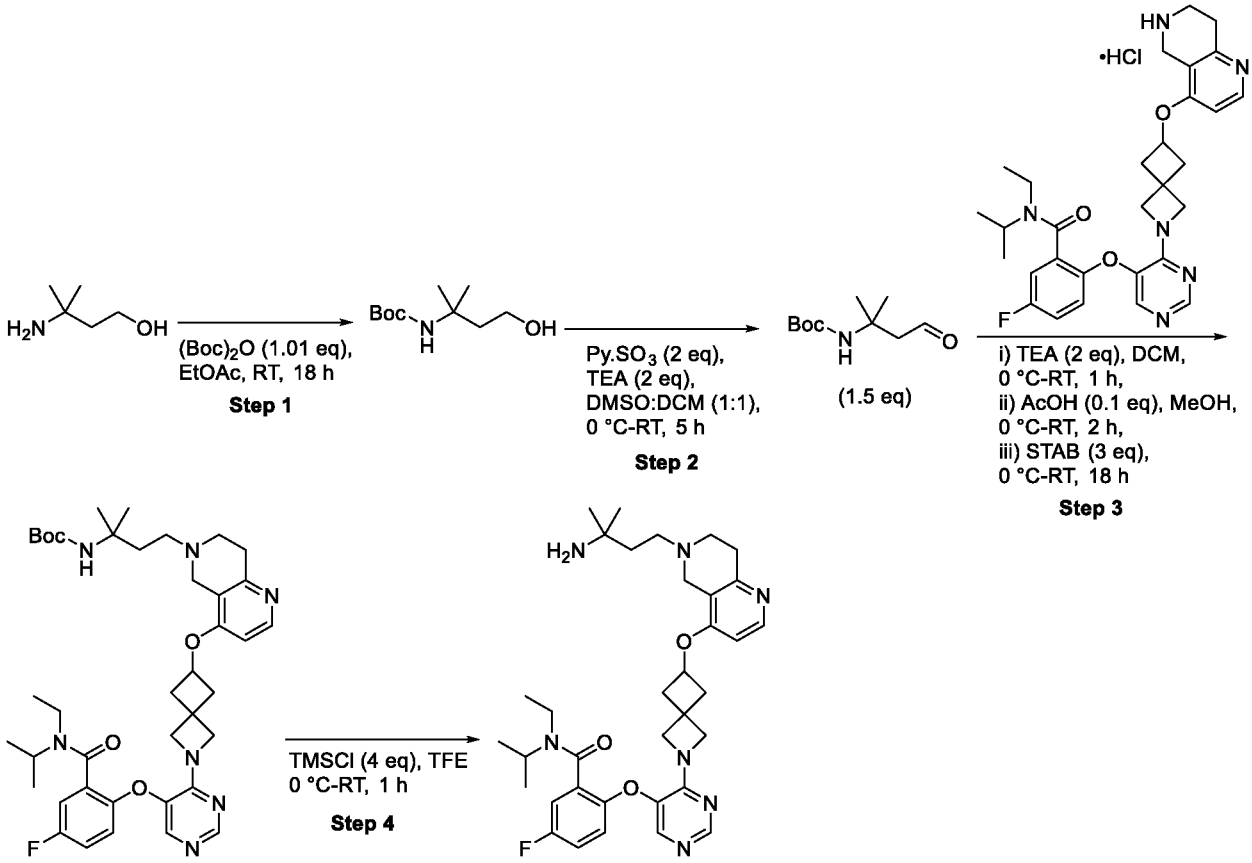


Step 3 was performed following the same procedure in two batches, 140 mg and 20 mg batches .

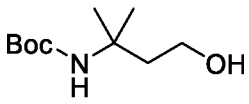
In a 20 mL pressure vial, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.140 g, 0.232 mmol) was added in DMF (0.6 mL). To this solution, dimethylglycine hydrochloride (0.061 g, 0.441 mmol), DIPEA (0.202 mL, 1.159 mmol), and HATU (0.176 g, 0.464 mmol) were added at RT. The reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction mixtures from both batches were combined for workup and purification. The reaction was diluted with water (20 mL) and extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AB) to obtain the product. The product was impure, and therefore was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(2-(2-(dimethylamino)-*N*-methylacetamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (13.92 g, 7.6% yield, combined yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 - 8.26 (m, 1H), 8.18 (t, J = 5.3 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.33 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.70 - 6.64 (m, 1H), 4.81 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H),

3.82 - 3.66 (m, 1H), 3.59 (br t, J = 6.6 Hz, 1H), 3.54 - 3.37 (m, 4H), 3.27 - 3.14 (m, 2H), 3.09 - 3.01 (m, 3H), 2.84 - 2.69 (m, 8H), 2.61 (br t, J = 6.6 Hz, 1H), 2.30 - 2.19 (m, 2H), 2.18 - 2.12 (m, 6H), 1.21 - 0.97 (m, 9H); LCMS (Method D): RT = 1.75 min, m/z = 689.4 $[M+H]^+$; HPLC (Method A): Rt = 4.62 min, 98.05%.

Example 294. 2-((4-(6-((6-(3-Amino-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 184)

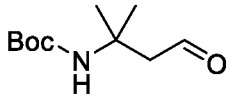


Step 1. tert-Butyl (4-hydroxy-2-methylbutan-2-yl)carbamate



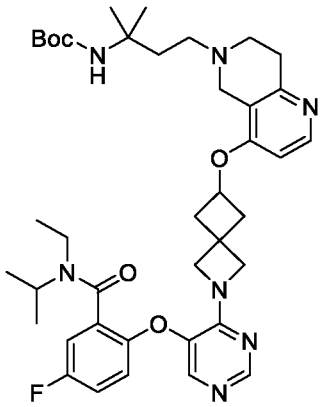
To a solution of 3-amino-3-methylbutan-1-ol (1 g, 9.69 mmol) in EtOAc (10 mL), Boc anhydride (2.273 mL, 9.79 mmol) was added portion-wise at RT. The reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure to obtain crude *tert*-butyl (4-hydroxy-2-methylbutan-2-yl)carbamate (2.1 g, quantitative) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.41 (br s, 1H), 4.41 (t, J = 4.9 Hz, 1H), 3.46 (dt, J = 5.1, 6.9 Hz, 2H), 1.72 (t, J = 6.9 Hz, 2H), 1.37 (s, 9H), 1.19 (s, 6H). This material was used without further purification.

Step 2. tert-Butyl (2-methyl-4-oxobutan-2-yl)carbamate



To a stirred solution of *tert*-butyl (4-hydroxy-2-methylbutan-2-yl)carbamate (500 mg, 2.460 mmol) in a mixture of DMSO:DCM (1:1, 10 mL), TEA (0.686 mL, 4.92 mmol) and pyridine-sulfur trioxide complex (783 mg, 4.92 mmol) were added at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 5 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). The reaction was diluted with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (3 x 25 mL). The combined organic layer was washed with sodium thiosulfate solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl (2-methyl-4-oxobutan-2-yl)carbamate (360 mg, 72.7% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (t, *J* = 2.5 Hz, 1H), 2.87 (d, *J* = 2.0 Hz, 2H), 1.45 (s, 9H), 1.39 (s, 6H), one proton was not visible. This material was used without further purification.

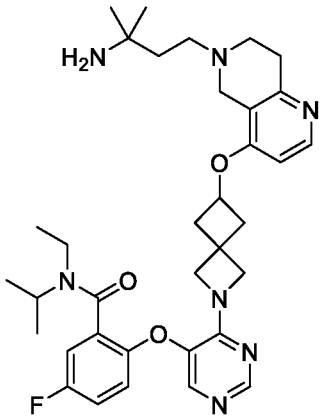
Step 3. tert-Butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-methylbutan-2-yl)carbamate



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride (200 mg, 0.343 mmol) in DCM (5 mL), TEA (0.096 mL, 0.686 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction was concentrated under reduced pressure. The crude residue was dissolved in MeOH (5 mL), and *tert*-butyl (2-methyl-4-oxobutan-2-yl)carbamate (104 mg, 0.514 mmol) and AcOH (1.964 µL, 0.034 mmol) were added at 0 °C. The reaction was stirred at RT for 2 h. To this reaction mixture, sodium triacetoxyborohydride (218 mg, 1.029 mmol) was added at 0 °C. The reaction was stirred at RT for 18 h. The reaction progress was monitored by TLC (10% MeOH in DCM).

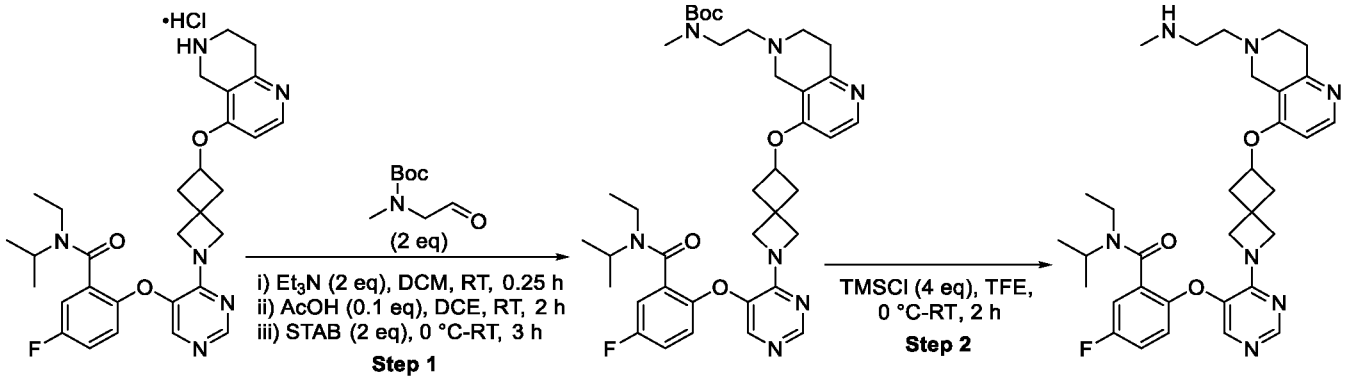
The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain *tert*-butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-methylbutan-2-yl)carbamate (200 mg, 34.9% yield). LCMS (Method B): Rt = 1.81 min, m/z = 732.3 $[M+H]^+$; 43.75%.

Step 4. 2-((4-(6-((6-(3-Amino-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

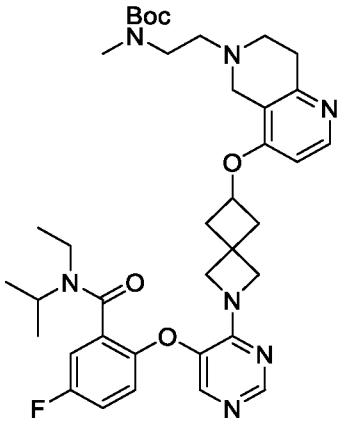


To a stirred solution of *tert*-butyl (4-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-methylbutan-2-yl)carbamate (200 mg, 0.273 mmol) in 2,2,2-trifluoroethanol (5 mL), TMSCl (0.140 mL, 1.093 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method A) to obtain 2-((4-(6-((6-(3-amino-3-methylbutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (19 mg, 10.79% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 - 7.66 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.79 - 4.68 (m, 1H), 4.46 - 4.07 (m, 4H), 3.81 - 3.70 (m, 1H), 3.41 (s, 2H), 3.40 - 3.35 (m, 1H), 3.29 - 3.09 (m, 2H), 2.83 - 2.72(m, 4H), 2.69 - 2.65 (m, 2H), 2.59 - 2.54 (m, 3H), 2.31 - 2.21 (m, 2H), 1.58 - 1.50 (m, 2H), 1.22 - 0.96 (m, 14H), one proton merged with solvent peak; LCMS (Method D): Rt = 1.75 min, m/z = 632.4 $[M+H]^+$; HPLC (Method A): Rt = 5.05 min, 98.07%.

Example 295. ***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)**benzamide (Compound No. 160)



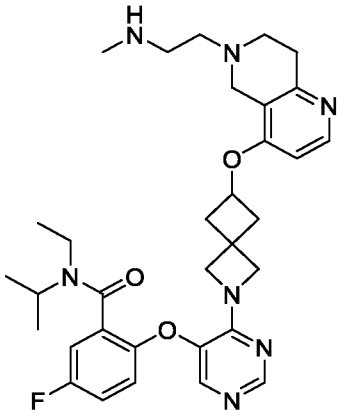
Step 1. tert-Butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)(methyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 2 equivalents of *tert*-butyl methyl(2-oxoethyl)carbamate, 0.1 equivalent of AcOH and 2 equivalents of STAB were used. The reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)(methyl)carbamate as a solid.

Yield: 43.0%; LCMS (Method G): Rt = 1.96 min, m/z = 704.6 $[M+H]^+$, 98.47%.

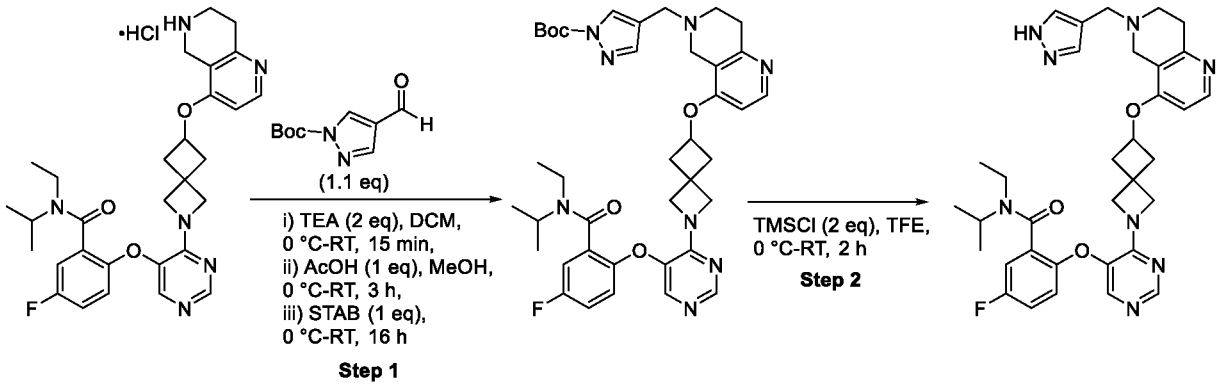
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



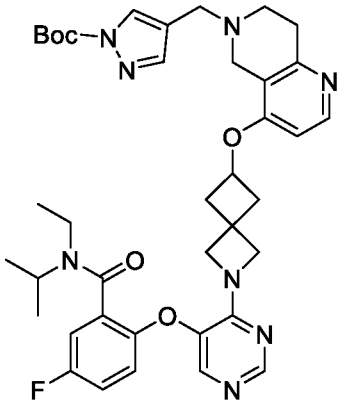
This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl (2-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)(methyl)carbamate. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(2-(methylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 24.34%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.22 - 8.15 (m, 1H), 7.79 - 7.63 (m, 1H), 7.34 - 7.19 (m, 2H), 7.11 - 6.99 (m, 1H), 6.68 - 6.64 (m, 1H), 4.80 - 4.67 (m, 1H), 4.49 - 4.04 (m, 4H), 3.75-3.78 (m, 1H), 3.43 (br s, 1H) 3.39- 3.37 (m, 2H), 3.28 - 3.10 (m, 1H), 2.85 - 2.73 (m, 4H), 2.73 - 2.66 (m, 2H), 2.63 - 2.59 (m, 2H), 2.57 - 2.53 (m, 3H), 2.30 (s, 3H), 2.28 - 2.20 (m, 2H), 1.30 - 0.91 (m, 9H); LCMS (Method B): Rt = 1.43 min, m/z = 604.4 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 99.47%.

Example 296. 2-((4-(6-((6-((1H-Pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 78)



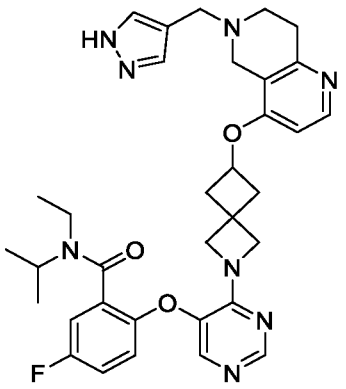
Step 1. tert-Butyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)-1H-pyrazole-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.1 equivalents of *tert*-butyl 4-formyl-1H-pyrazole-1-carboxylate was used. The reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 80% EtOAc in hexane) to obtain *tert*-butyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)-1H-pyrazole-1-carboxylate as a solid.

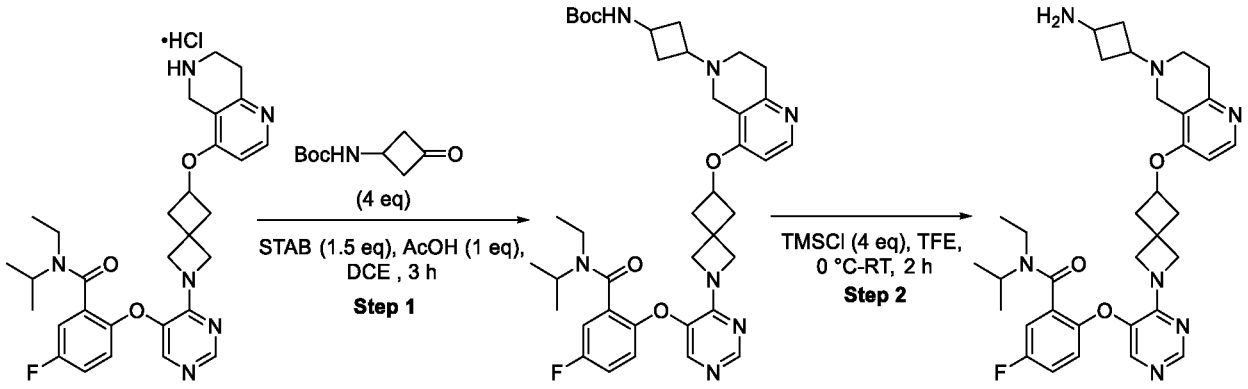
Yield: 54.8%; LCMS (Method G): Rt = 1.96 min, m/z = 727.4 $[M+H]^+$; 91.22%.

Step 2. 2-((4-(6-((6-((1H-Pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

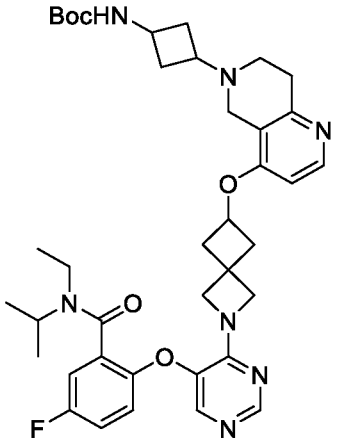


In a dried, 50 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl 4-((4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)-1H-pyrazole-1-carboxylate (150 mg, 0.206 mmol) was added in 2,2,2-trifluoroethanol (3 mL). TMSCl (0.053 mL, 0.413 mmol) was added to this solution at 0 °C, and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-((1H-pyrazol-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (33.81 mg, 25.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.68 (br s, 1H), 8.31 - 8.26 (m, 1H), 8.20 - 8.15 (m, 1H), 7.77 - 7.67 (m, 1H), 7.66 (br s, 1H), 7.42 (br s, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.00 (m, 1H), 6.68 - 6.64 (m, 1H), 4.76 - 4.68 (m, 1H), 4.46 - 4.07 (m, 4H), 3.81 - 3.71 (m, 1H), 3.58 (s, 2H), 3.42 (s, 2H), 3.40 - 3.35 (m, 1H), 3.28 - 3.12 (m, 2H), 2.82 - 2.73 (m, 4H), 2.67 - 2.62 (m, 1H), 2.27 - 2.19 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method B): Rt = 1.47 min, m/z = 627.2 $[M+H]^+$; HPLC (Method A): Rt = 4.80 min, 99.86%.

Example 297. 2-((4-(6-((6-(3-Aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 171)



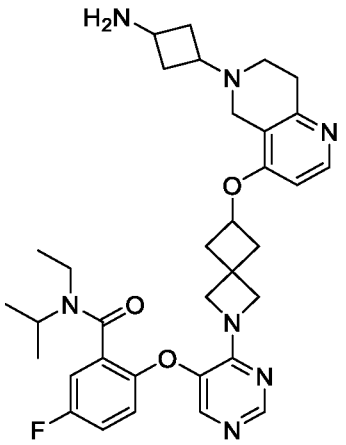
Step 1. tert-Butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)cyclobutyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 4 equivalents of *tert*-butyl (3-oxocyclobutyl)carbamate, 1.5 equivalents of STAB and 1 equivalent of AcOH were used, and DCE was used as a solvent. After completion, the reaction was quenched with 10% $NaHCO_3$ solution and extracted with 10% MeOH in DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 6% MeOH in DCM) to afford *tert*-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)cyclobutyl)carbamate as a solid.

Yield: 63.8%; LCMS (Method G): Rt = 1.96 min, m/z = 716.4 $[M+H]^+$, 93.32%.

Step 2. 2-((4-(6-((6-(3-Aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

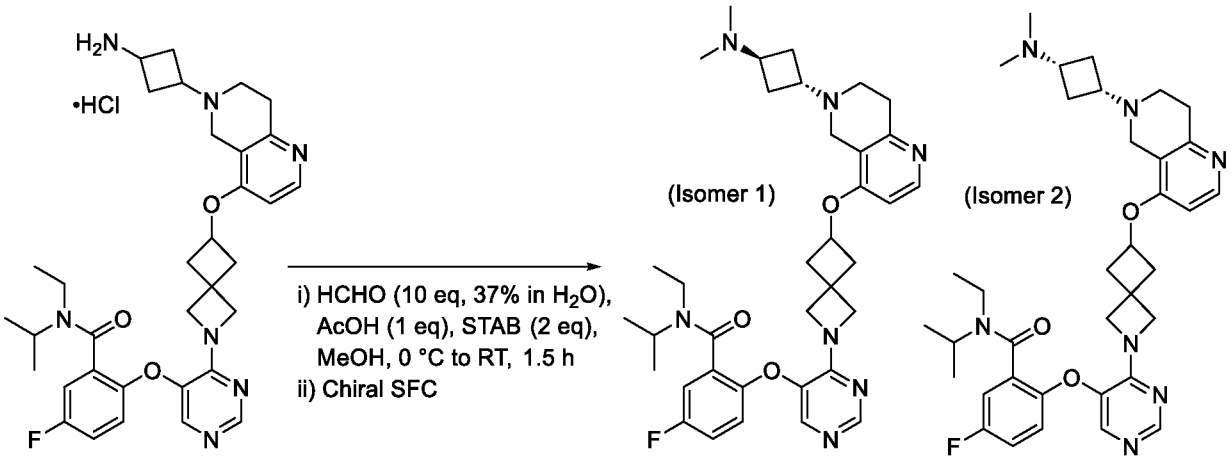


This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl (3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)cyclobutyl)carbamate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure to afford crude 2-((4-(6-((6-(3-aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-(3-aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 77%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.79 - 7.64 (m, 1H), 7.34 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.70 - 6.63 (m, 1H), 4.81 - 4.69 (m, 1H), 4.32 - 4.07 (m, 4H), 3.75 (spt, J = 6.6 Hz, 1H), 3.45 - 3.38 (m, 2H), 3.31 - 3.11 (m, 3H), 3.08 - 2.90 (m, 1H), 2.85 - 2.71 (m, 4H), 2.58 - 2.52 (m, 3H), 2.46 - 2.35 (m, 1H), 2.32 - 2.20 (m, 2H), 2.18 - 1.93 (m, 2H), 1.84 - 1.70 (m, 1H), 1.56 - 1.43 (m, 1H), 1.28 - 0.94 (m, 9H); LCMS (Method F): Rt = 1.65 and 1.67 min, m/z = 616.4 $[M+H]^+$; HPLC (Method A): Rt = 4.38 min, 54.05%, Rt = 4.51 min, 45.53%; Chiral SFC (Method K): Peak 1: Rt = 4.35 min, 56.07%; Peak 2: Rt = 4.61 min, 43.93%.

Example 298. (*E1*)-2-((4-(6-((6-(3-Aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 177-a)

Example 299. (*E2*)-2-((4-(6-((6-(3-Aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 178-a)



This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with 2-((4-(6-((6-(3-aminocyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 10 equivalents of formaldehyde (37 wt% in H_2O) was used and MeOH was used as the solvent. After completion, the reaction was concentrated under reduced pressure. 10% $NaHCO_3$ solution was added to the crude and the mixture was extracted with EtOAc. The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude 2-((4-(6-((6-(3-(dimethylamino)cyclobutyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (290 mg, 82% yield) as a solid. LCMS (Method B): Rt = 1.31 min, m/z = 644.2 $[M+H]^+$, 98.06%. This crude diastereomeric mixture was purified using Chiral Prep SFC (Method D) to obtain both isomers.

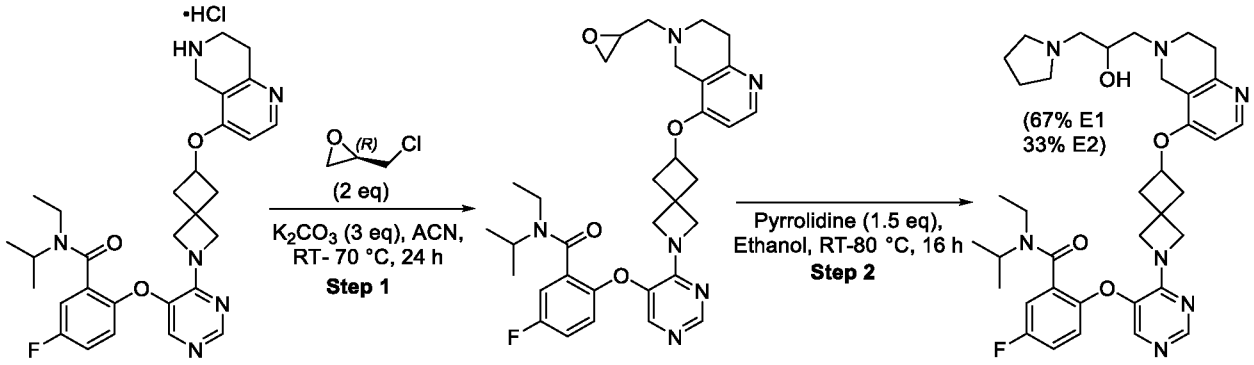
Isomer 1. Yield: 12.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.63 (m, 1H), 4.80 - 4.69 (m, 1H), 4.33 - 4.06 (m, 4H), 3.75 (m, J = 6.6 Hz, 1H), 3.46 - 3.37 (m, 1H), 3.30 (s, 2H), 3.29 - 3.08 (m, 1H), 2.90 (quin, J = 6.4 Hz, 1H), 2.84 - 2.73 (m, 4H), 2.64 - 2.53 (m, 3H), 2.31 - 2.20 (m, 2H), 2.05 (s, 6H), 2.03 - 1.96 (m, 2H), 1.41 - 0.90 (m, 11H); LCMS (Method B): Rt = 1.34 min, m/z = 644.2 $[M+H]^+$; HPLC (Method A): Rt = 4.65 min, 98.58%; Chiral SFC (Method AA) Rt = 4.96 min, 99.45%.

Isomer 2. Yield: 37.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.20 - 8.14 (m, 1H), 7.77 - 7.64 (m, 1H), 7.35 - 7.22 (m, 2H), 7.11 - 6.99 (m, 1H), 6.71 - 6.63 (m, 1H),

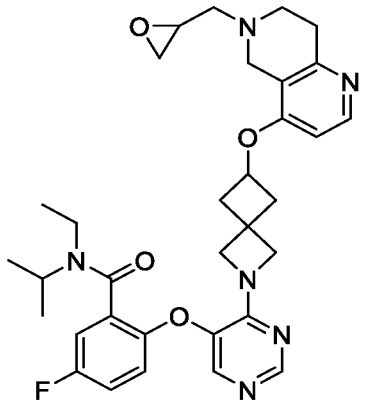
4.81 - 4.66 (m, 1H), 4.31 - 4.06 (m, 4H), 3.80 - 3.71 (m, 1H), 3.47 - 3.35 (m, 1H), 3.31 (s, 2H), 3.28 - 3.08 (m, 1H), 2.85 - 2.71 (m, 4H), 2.63 - 2.52 (m, 3H), 2.35 - 2.19 (m, 5H), 2.03 (m, 6H), 1.67 - 1.55 (m, 2H), 1.23 - 0.96 (m, 9H); LCMS (Method B): Rt = 1.36 min, m/z = 644.2 $[M+H]^+$; HPLC (Method A): Rt = 4.92 min, 97.00%;

Chiral SFC (Method AA) Rt = 7.14 min, 96.69%.

Example 300. *N*-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 140)



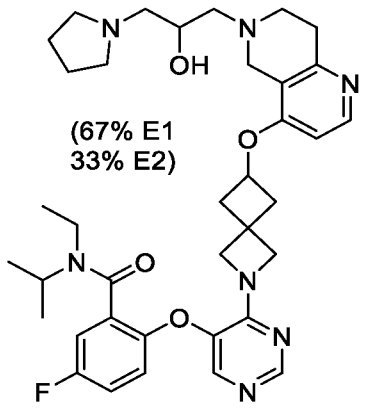
Step 1. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (300 mg, 0.549 mmol) in ACN (3 mL), powdered K_2CO_3 (265 mg, 1.921 mmol) and (*R*)-2-(chloromethyl)oxirane (50.8 mg, 0.549 mmol) were added. The reaction was stirred at RT for 24 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC (10% MeOH in DCM). The starting material was not consumed. Therefore, one more equivalent of (*R*)-2-(chloromethyl)oxirane (50.8 mg, 0.549 mmol) was added and the reaction was continued for another 5 h. After completion, the reaction was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method D) to afford *N*-ethyl-5-fluoro-*N*-

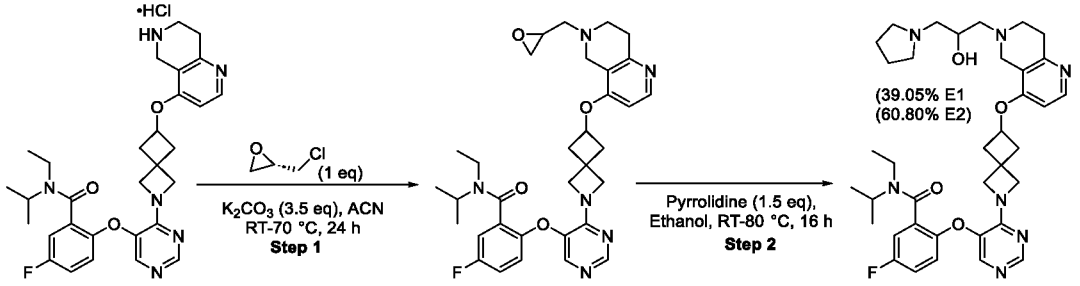
isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (40 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.82 - 4.70 (m, 1H), 4.34 - 4.06 (m, 4H), 3.75 (spt, J = 6.6 Hz, 1H), 3.62 - 3.39 (m, 2H), 3.27 - 3.05 (m, 3H), 2.95 - 2.70 (m, 7H), 2.43 - 2.35 (m, 2H), 2.31 - 2.17 (m, 3H), 1.36 - 0.95 (m, 9H); LCMS (Method G): Rt = 1.65 min, m/z = 603.5 $[M+H]^+$, 97.48%.

Step 2. N-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

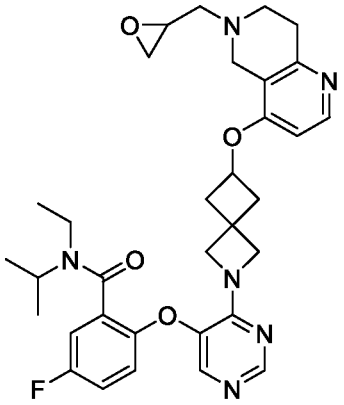


To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (40 mg, 0.066 mmol) in ethanol (0.2 mL), pyrrolidine (0.0082 µL, 0.100 mmol) was added at RT. The reaction was stirred at 80 °C for 16 h. The progress of the reaction was monitored by TLC (30% MeOH DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method B) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (8 mg, 17.71% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.79 - 7.65 (m, 1H), 7.33 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.63 (m, 1H), 4.80 - 4.68 (m, 1H), 4.35 - 4.06 (m, 5H), 3.84 - 3.69 (m, 2H), 3.50 (s, 2H), 3.44 - 3.39 (m, 1H), 3.26 - 3.11 (m, 2H), 2.86 - 2.72 (m, 6H), 2.63 - 2.57 (m, 1H), 2.48 - 2.42 (m, 4H), 2.38 - 2.32 (m, 2H), 2.31 - 2.20 (m, 2H), 1.73 - 1.60 (m, 4H), 1.30 - 0.93 (m, 9H); LCMS (Method G): Rt = 1.67 min, m/z = 674.4 $[M+H]^+$, 99.43% ; HPLC (Method A): Rt = 5.33 min, 97.76%; Chiral SFC (Method C) Peak-1: Rt = 7.44 min, 66.93%, Peak-2: 9.19 min, 33.06%.

Example 301. ***N*-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide** (Compound No. 135)

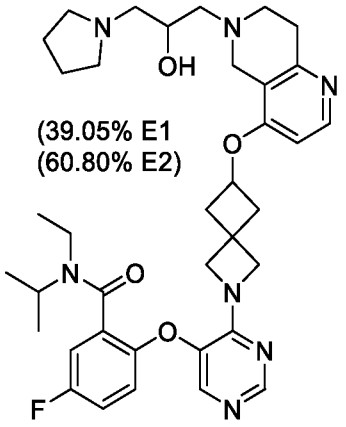


Step 1. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 300, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 1 equivalent of (*S*)-2-(chloromethyl)oxirane and 3.5 equivalents of powdered K_2CO_3 were used, and the reaction was stirred at 70 °C. The reaction was filtered and washed with ACN, and the filtrate was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a semi-solid. This material was used without further purification. Yield: 49.9%; LCMS (Method G): Rt = 1.67, m/z = 603.5 $[M+H]^+$, 66.04%.

Step 2. N-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



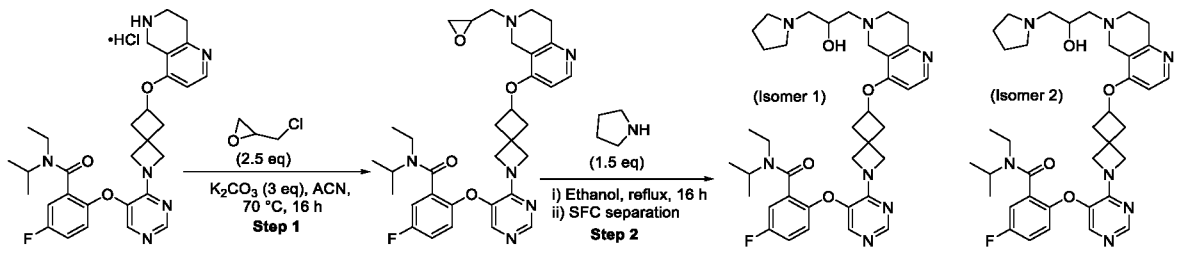
This compound was synthesized following the procedure described for the synthesis of Example 300, step 2, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide. The crude was purified by Prep HPLC (Method I) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(1006yrrolidine-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 6.22%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 – 8.26 (m, 1H), 8.20 – 8.16 (m, 1H), 7.77 – 7.66 (m, 1H), 7.33 – 7.22 (m, 2H), 7.10 – 7.00 (m, 1H), 6.68 – 6.64 (m, 1H), 4.79 – 4.69 (m, 1H), 4.47 – 4.06 (m, 6H), 3.84 – 3.69 (m, 2H), 3.50 (s, 2H), 3.44 – 3.37 (m, 1H), 3.27 – 3.11 (m, 2H), 2.84 – 2.72 (m, 6H), 2.62 – 2.55 (m, 2H), 2.47 – 2.35 (m, 4H), 2.29 – 2.21 (m, 2H), 1.69 – 1.64 (m, 4H), 1.26 – 0.97 (m, 9H);

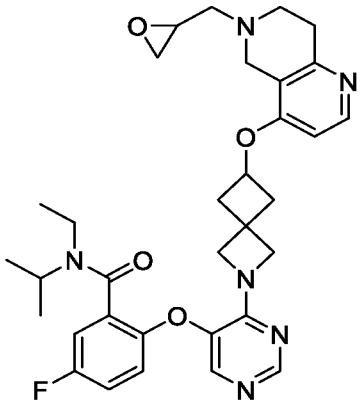
LCMS (Method G): Rt = 1.62 min, 674.4 $[M+H]^+$; HPLC (Method A): RT = 5.29 min, 98.05%. Chiral SFC (Method J): Peak-1: RT = 7.57, 39.05%; Peak-2: RT = 9.29 min, 60.80%.

Example 302. (*E1*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound 165)

Example 303. (*E2*)-*N*-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 173)

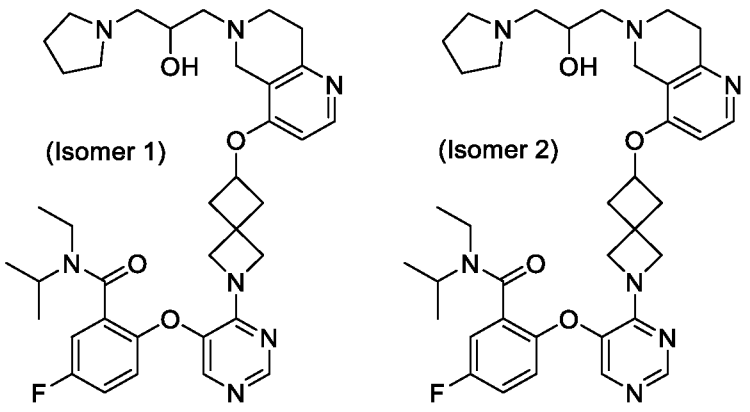


Step 1. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 300, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 2.5 equivalents of (±)-2-(chloromethyl)oxirane was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.836 g, 18.60% yield). LCMS (Method B): Rt = 1.51, m/z = 603.2 $[M+H]^+$, 23.44%. This material was used without further purification.

Step 2. (E1)-N-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide and (E2)-N-Ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 300, step 2, starting with (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(oxiran-2-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.09 g, 9.07% yield). LCMS (Method G): Rt = 1.65 min, m/z = 674.2 $[M+H]^+$, 96.91%. Chiral SFC: (Method J): Rt = 7.59 min and 9.31 min; 50.25% and 49.74%.

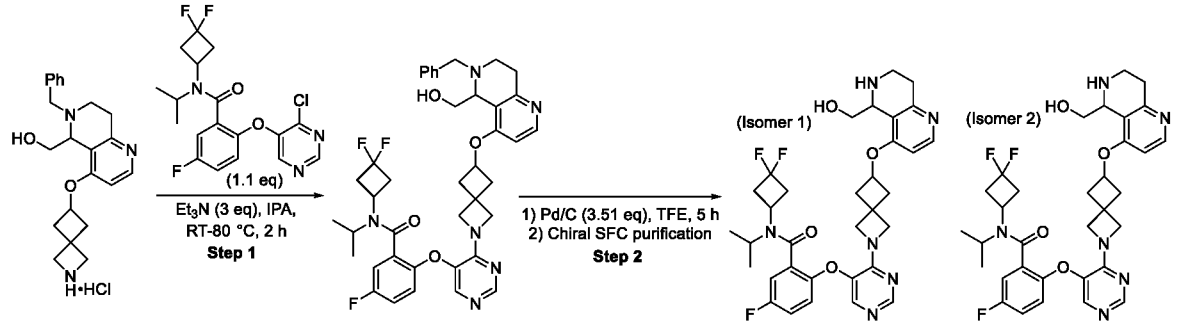
(±)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (90 mg) was purified by chiral Prep SFC (Method H) to obtain both isomers. (*E1*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.04 g, 43.7% yield) and (*E2*)-*N*-ethyl-5-fluoro-2-((4-(6-((6-(2-hydroxy-3-(pyrrolidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (0.025 g, 27.7% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.24 (m, 1H), 8.21 - 8.15 (m, 1H), 7.78 - 7.64 (m, 1H), 7.34 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.67 - 6.64 (m, 1H), 4.81 - 4.67 (m, 1H), 4.46 - 4.07 (m, 4H), 3.85 - 3.68 (m, 2H), 3.50 (br s, 2H), 3.46-3.39 (m, 1H), 3.31 - 3.10 (m, 1H), 2.85 - 2.71 (m, 6H), 2.60 - 2.52 (m, 4H), 2.49 - 2.39 (m, 4H), 2.30 - 2.18 (m, 2H), 1.72 - 1.59 (m, 4H), 1.22 - 0.87 (m, 9H), -OH proton was not observed; LCMS (Method B): Rt = 1.33 min, 674.2 $[M+H]^+$; HPLC (Method A): RT = 4.55 min, 98.42%. Chiral SFC (Method J): RT = 7.93 min, 100%.

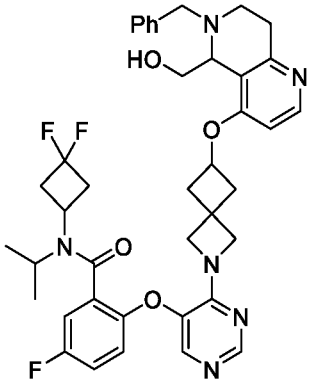
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.31 - 8.25 (m, 1H), 8.22 - 8.12 (m, 1H), 7.80 - 7.65 (m, 1H), 7.35 - 7.20 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.63 (m, 1H), 4.80 - 4.66 (m, 1H), 4.48 - 4.04 (m, 4H), 3.85 - 3.69 (m, 2H), 3.50 (br s, 2H), 3.43 - 3.35 (m, 1H), 3.27 - 3.12 (m, 1H), 2.84 - 2.71 (m, 6H), 2.60 - 2.53 (m, 4H), 2.48 - 2.34 (m, 4H), 2.30 - 2.17 (m, 2H), 1.73 - 1.60 (m, 4H), 1.23 - 0.98 (m, 9H), -OH proton not observed; LCMS (Method G): Rt = 1.79 min, 674.7 $[M+H]^+$; HPLC (Method A): RT = 4.59 min, 99.63%; Chiral SFC (Method J): RT = 10.05 min, 100%.

Example 304. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 306)

Example 305. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 307)



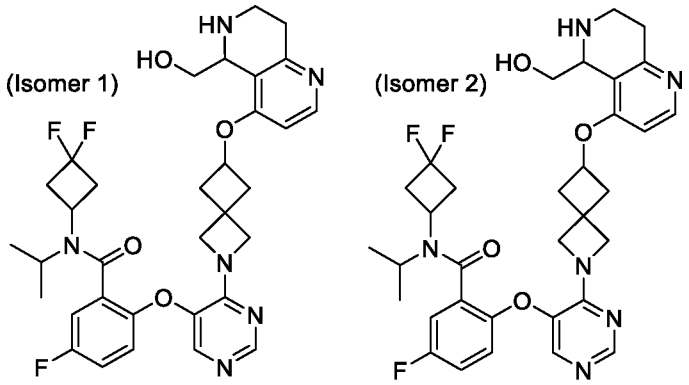
Step 1. (±)-2-((4-(6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-Tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1 equivalent of (±)-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanol hydrochloride and 1.1 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of TEA were used. After completion, the reaction was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 100% EtOAc) to obtain (±)-2-((4-(6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-

isopropylbenzamide (0.7 g, 58.7% yield) as a solid. LCMS (Method B): Rt = 1.35 min, m/z = 729.3 $[M+H]^+$, 76.08%.

Step 2. (E1)-N-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide and (E2)-N-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



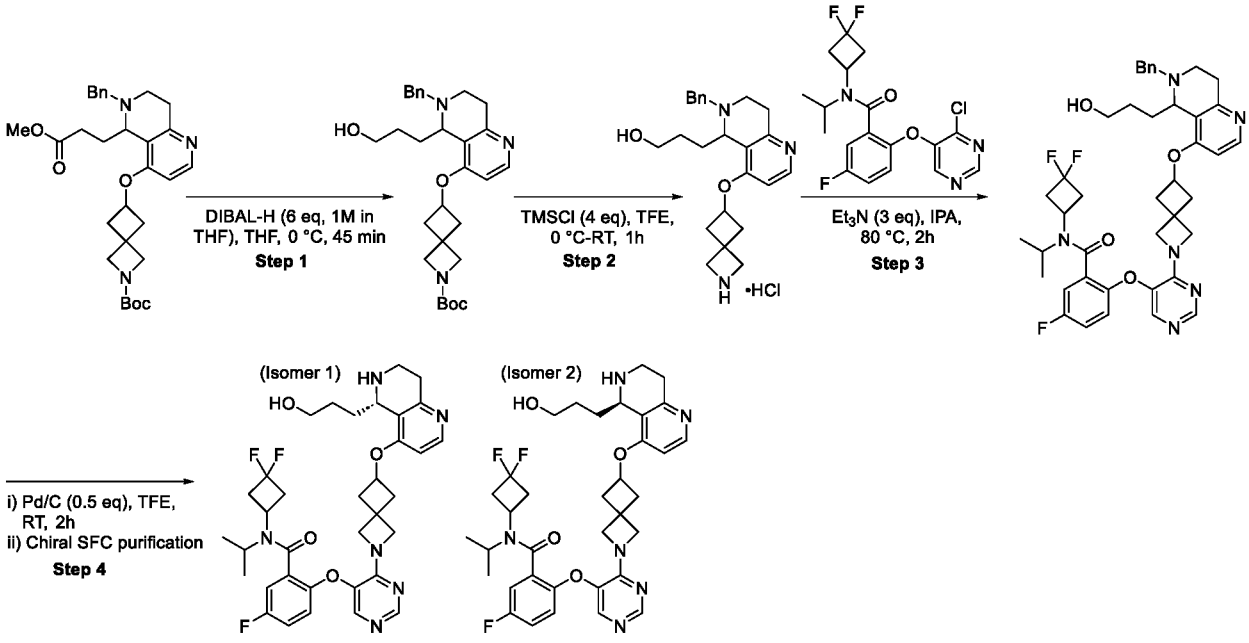
To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (0.7 g, 0.960 mmol) in TFE (4 mL), Pd-C (0.359 g, 3.37 mmol) was added at RT. The reaction was stirred at RT for 5 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH/DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain crude *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide. This compound was purified by chiral Prep SFC (Method M) to obtain both isomers, (*E1*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (38.19 mg, 0.058 mmol, 6.04% yield) and (*E2*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (39.12 mg, 0.059 mmol, 6.19% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 (s, 1H), 7.36 (dd, J = 2.8, 8.1 Hz, 1H), 7.27 (dt, J = 2.9, 8.6 Hz, 1H), 7.06 (dd, J = 4.3, 8.9 Hz, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.73 (quin, J = 6.7 Hz, 1H), 4.67 - 4.58 (m, 1H), 4.35 - 4.06 (m, 4H), 4.00 - 3.83 (m, 2H), 3.81 - 3.64 (m, 2H), 3.63 - 3.41 (m, 3H), 3.16 - 3.02 (m, 1H), 2.94 - 2.62 (m, 8H), 2.29 - 2.18 (m, 2H), 1.10 (d, J = 5.9 Hz, 3H), 1.01 (d, J = 6.0 Hz, 3H); LCMS (Method G): Rt = 1.68 min, m/z = 639.6 $[M+H]^+$; HPLC (Method A): Rt = 4.80 min, 97.53%; SFC (Method J): Rt = 2.18 min, 100%.

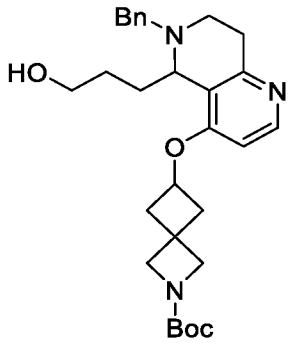
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (br d, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.36 (br d, J = 5.3 Hz, 1H), 7.28 (br t, J = 8.3 Hz, 1H), 7.12 - 7.02 (m, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.73 (quin, J = 6.4 Hz, 1H), 4.69 - 4.59 (m, 1H), 4.36 - 4.03 (m, 4H), 4.00 - 3.85 (m, 2H), 3.82 - 3.64 (m, 2H), 3.63 - 3.40 (m, 3H), 3.17 - 2.99 (m, 1H), 2.94 - 2.63 (m, 8H), 2.31 - 2.19 (m, 2H), 1.10 (d, J = 5.4 Hz, 3H), 1.01 (d, J = 5.3 Hz, 3H); LCMS (Method G): Rt = 1.68 min, m/z = 639.6 $[M+H]^+$; HPLC (Method A): Rt = 4.80 min, 97.75%; SFC (Method J): Rt = 3.30 min, 99.44%.

Example 306. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 304)

Example 307. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 305)

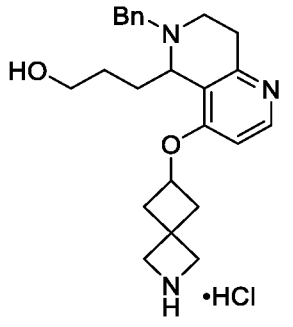


Step 1. (±)-tert-Butyl 6-((6-benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



In a dried, 50 mL two neck round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 6-((6-benzyl-5-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (0.4 g, 0.767 mmol) was dissolved in THF (5 mL). To this solution, DIBAL-H (4.60 mL, 4.60 mmol, 1M in THF) was added at 0 °C, and the reaction was stirred at the same temperature for 45 min. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (30 mL) and extracted with EtOAc (20 x 3 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column using EtOAc in (product eluted at 6% EtOAc in hexane) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (250 mg, 51.1% yield) as a viscous liquid. LCMS (Method G): Rt = 2.11 min, m/z = 494.3 $[M+H]^+$, 77.39%.

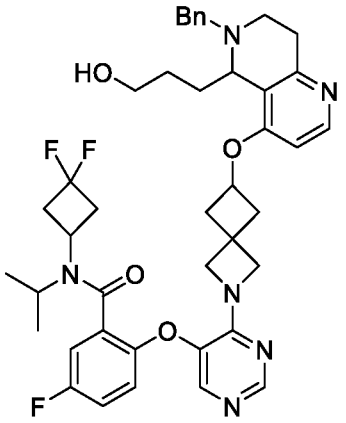
Step 2. (±)-3-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propan-1-ol hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with (±)-*tert*-butyl 6-((6-benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. After completion, the reaction was concentrated under reduced pressure. The crude was triturated with EtOAc, the organic layer was decanted and the solid was dried under vacuum to afford

(±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propan-1-ol hydrochloride (0.210 g, 78% yield) as a solid. LCMS (Method G): Rt = 1.50 min, m/z = 394.2 $[M+H]^+$, 77.78%.

Step 3. (±)-2-((4-(6-((6-Benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

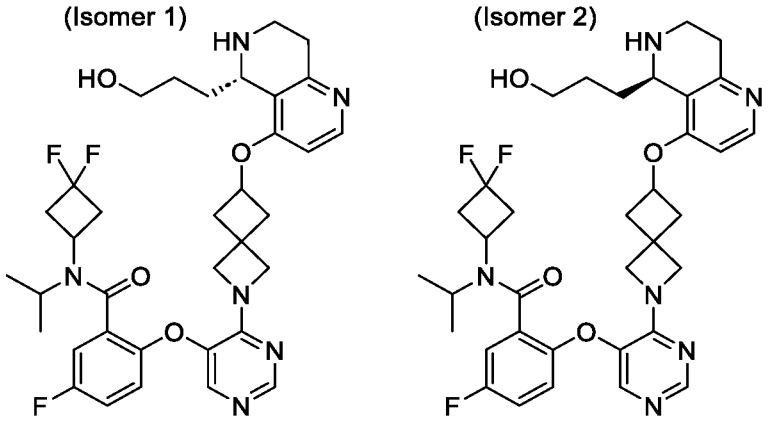


This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1 equivalent of (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)propan-1-ol and 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of TEA was used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 4% MeOH in DCM) to obtain (±)-2-((4-(6-((6-benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (230 mg, 44.7% yield) as a solid. LCMS (Method G): Rt = 2.10 min, m/z = 757.7 $[M+H]^+$, 78.52%.

Step 4. (E1)-N-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide and (E2)-N-(3,3-Difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-

hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide

(Isomer 1) (Isomer 2)



In a dried, 25 mL round bottom flask under a nitrogen atmosphere, (±)-2-((4-(6-((6-benzyl-5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (220 mg, 0.291 mmol) was added in TFE (2 mL). Pd-C (155 mg, 0.145 mmol) was added to this solution, and the reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (110 mg, 56.1% yield) as a solid. LCMS (Method G): Rt = 1.71 min, m/z = 667.6 $[M+H]^+$, 98.86%. This racemic mixture was purified by chiral Prep SFC (Method F) to obtain both isomers, (*E1*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (22 mg, 16.84% yield) and (*E2*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-2-((4-(6-((5-(3-hydroxypropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (29 mg, 19.55% yield) as solids.

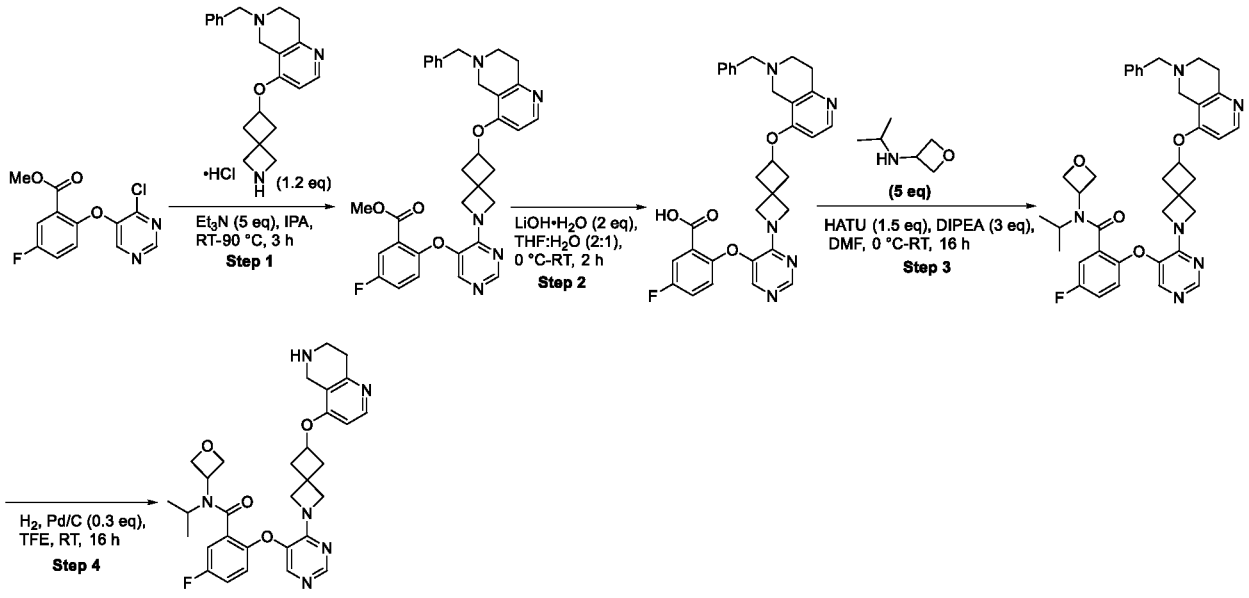
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.77 (s, 1H), 7.36 (dd, *J* = 2.9, 8.2 Hz, 1H), 7.27 (dt, *J* = 3.0, 8.6 Hz, 1H), 7.06 (br dd, *J* = 4.2, 8.9 Hz, 1H), 6.63 (d, *J* = 5.7 Hz, 1H), 4.73 (quin, *J* = 6.4 Hz, 2H), 4.40 - 4.01 (m, 4H), 3.97 - 3.81 (m, 2H), 3.80 - 3.37 (m, 5H), 3.08 - 2.97 (m, 1H), 2.95 - 2.87 (m, 1H), 2.84 - 2.61 (m, 7H), 2.30 -

2.14 (m, 2H), 1.73 - 1.50 (m, 4H), 1.10 (br d, *J* = 6.1 Hz, 3H), 1.01 (br d, *J* = 5.9 Hz, 3H); LCMS (Method G): Rt = 1.75 min, m/z = 667.6 $[M+H]^+$; HPLC (Method A): Rt = 5.13 min, 99.92%; Chiral SFC (Method AF): Rt = 7.02 min, 98.56%.

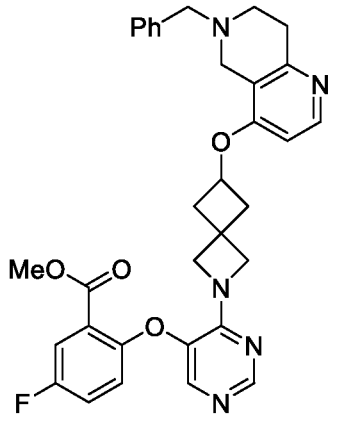
Isomer 2. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.30 (s, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.77 (s, 1H), 7.36 (dd, *J* = 2.8, 8.1 Hz, 1H), 7.27 (dt, *J* = 2.9, 8.6 Hz, 1H), 7.06 (dd, *J* = 4.1, 8.9 Hz, 1H), 6.63 (d, *J* = 5.5 Hz, 1H), 4.73 (quin, *J* = 6.4 Hz, 2H), 4.42 - 4.03 (m, 4H), 3.99 - 3.65 (m, 4H), 3.61 - 3.37 (m, 3H), 3.08 - 2.97 (m, 1H), 2.95 - 2.87 (m, 1H), 2.84 - 2.61 (m, 7H), 2.31 - 2.17 (m, 2H), 1.73 - 1.49 (m, 4H), 1.16 - 0.98 (m, 6H); LCMS (Method G): Rt = 1.75 min, m/z = 667.6 $[M+H]^+$; HPLC (Method A): Rt = 5.13 min, 99.08%; Chiral SFC (Method AF): Rt = 8.06 min, 97.44%.

Example 308. 5-Fluoro-*N*-isopropyl-*N*-(oxetan-3-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 342)

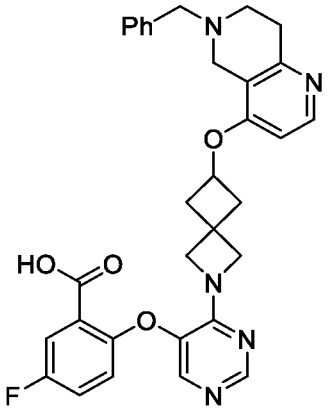


Step 1. Methyl 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate



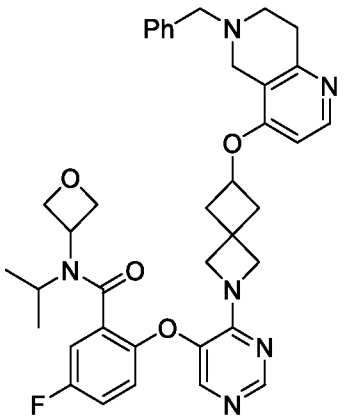
This compound was synthesized following the procedure described for the synthesis of Example 9, step 1, starting with 1 equivalent methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate, except that 1.2 equivalents of 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride and 5 equivalents of TEA were used. The reaction was stirred at 90 °C. After completion, the reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to afford methyl 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate as a solid.
Yield: 41.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.49 (ddd, J = 3.3, 7.9, 9.0 Hz, 1H), 7.38 - 7.30 (m, 4H), 7.32 - 7.24 (m, 1H), 7.11 (dd, J = 4.4, 9.1 Hz, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.72 (quin, J = 6.7 Hz, 1H), 4.26 (s, 2H), 4.16 (s, 2H), 3.81 (s, 3H), 3.67 (s, 2H), 3.45 (s, 2H), 2.85 - 2.73 (m, 4H), 2.72 - 2.66 (m, 2H), 2.27 - 2.17 (m, 2H); LCMS (Method G): Rt = 1.97 min, m/z = 582.2 $[M+H]^+$, 94.72%.

Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid



This compound was synthesized following the procedure described for the synthesis of Example 9, step 2, starting with 1 equivalent methyl 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate, except that 2 equivalents of $LiOH.H_2O$ was used, and 2:1 THF/H_2O was used as solvent. The organic solvent was removed under reduced pressure. The aqueous layer was acidified with 1.5 N HCl (pH~2) and the solvent was concentrated under reduced pressure. The crude was azeotroped with toluene to obtain crude 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid as a solid. This material was used without further purification.
Yield: 96%; LCMS (Method G): Rt = 1.47 min, m/z = 568.1 $[M+H]^+$, 94.61%.

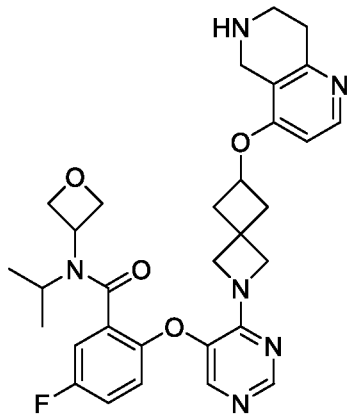
Step 3. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(oxetan-3-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic and 5 equivalents of *N*-isopropyloxetan-3-amine. The reaction was diluted with water and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(oxetan-3-yl)benzamide as a solid.

Yield: 34.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.82 - 7.76 (m, 1H), 7.38 - 7.32 (m, 5H), 7.31 - 7.23 (m, 2H), 7.08 - 7.01 (m, 1H), 6.66 (d, J = 5.8 Hz, 1H), 5.26 - 5.05 (m, 1H), 4.86 - 4.66 (m, 2H), 4.64 - 4.54 (m, 2H), 4.31 - 4.01 (m, 4H), 3.76 - 3.65 (m, 3H), 3.47 (s, 2H), 2.83 - 2.72 (m, 4H), 2.71 - 2.65 (m, 3H), 2.25 - 2.16 (m, 2H), 1.54 - 0.94 (m, 6H); LCMS (Method G): Rt = 2.00 min, m/z = 665.3 $[M+H]^+$, 97.40%.

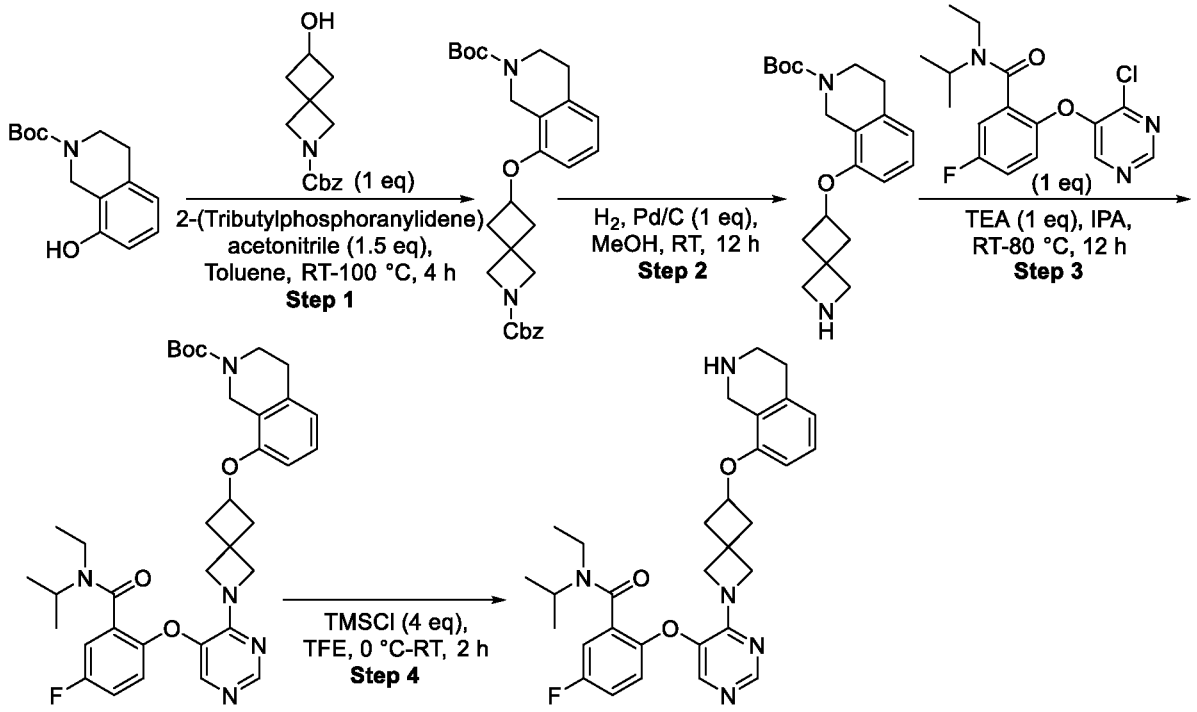
Step 4. 5-Fluoro-N-isopropyl-N-(oxetan-3-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



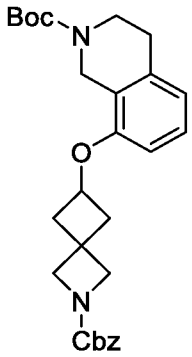
To a stirred solution of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(oxetan-3-yl)benzamide (200 mg, 0.301 mmol) in 2,2,2-trifluoroethanol (4 mL), Pd/C (96 mg, 0.090 mmol) was added at RT. The reaction was stirred at RT for 16 h under a hydrogen

atmosphere (balloon pressure). The reaction progress was monitored by TLC (20% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad. The pad was washed with 2,2,2-trifluoroethanol (2 x 20 mL) and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AE). The product fractions were concentrated under reduced pressure and lyophilized to afford a product. The isolated compound showed impurity. Therefore, the product was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (60 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-*N*-(oxetan-3-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (43.54 mg, 24.60% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.42 - 7.18 (m, 2H), 7.11 - 6.99 (m, 1H), 6.64 (d, J = 5.8 Hz, 1H), 5.28 - 5.07 (m, 1H), 4.85 - 4.68 (m, 2H), 4.66 - 4.51 (m, 2H), 4.31 - 4.05 (m, 4H), 3.78 - 3.65 (m, 3H), 2.95 (t, J = 5.7 Hz, 2H), 2.87 - 2.74 (m, 2H), 2.71 - 2.65 (m, 2H), 2.28 - 2.19 (m, 2H), 1.55 - 0.89 (m, 6H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.41 min, m/z = 575.2 $[M+H]^+$; HPLC (Method G): Rt = 4.14 min, 98.46%.

Example 309. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 12)



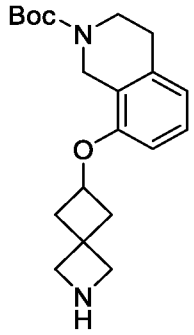
Step 1. tert-Butyl 8-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



To a stirred solution of *tert*-butyl 8-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.504 g, 2.022 mmol) and benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (0.500 g, 2.022 mmol) in toluene (10 mL), 2-(tributylphosphoranylidene)acetonitrile (0.689 g, 3.03 mmol) was added at RT. The reaction was stirred at 100 °C for 4 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was quenched with water (25 mL) and the mixture was extracted with EtOAc (3 x 35 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 25-30% EtOAc in hexane) to

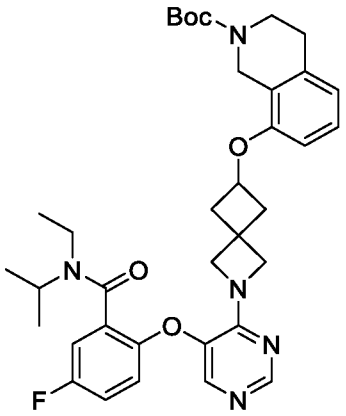
obtain *t*ert-butyl 8-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (550 mg, 51.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 - 7.29 (m, 5H), 7.10 (t, J = 7.9 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.67 - 6.62 (m, 1H), 5.02 (s, 2H), 4.69 - 4.60 (m, 1H), 4.34 (s, 2H), 4.08 - 3.93 (m, 2H), 3.52 (t, J = 5.5 Hz, 2H), 2.79 - 2.65 (m, 4H), 2.27 - 2.16 (m, 2H), 1.42 (s, 9H), two protons merged with solvent peaks; LCMS (Method D): Rt = 2.44 min, m/z = 479.1 $[M+H]^+$, 90.80%.

Step 2. tert-Butyl 8-((2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



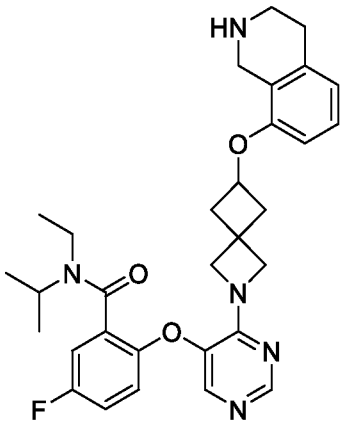
To a solution of *t*ert-butyl 8-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (550 mg, 1.149 mmol) in MeOH (20 mL), Pd/C (122 mg, 1.149 mmol) was added. The reaction was stirred at RT for 12 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction mixture was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 20 mL). The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 100% EtOAc in hexane) to obtain *tert*-butyl 8-((2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (325 mg, 59.4% yield) as a semisolid. LCMS (Method D): Rt = 1.99 min, m/z = 345.2 $[M+H]^+$, 72.42%.

Step 3. tert-Butyl 8-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of *tert*-butyl 8-((2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate and 1 equivalent of Et_3N were used. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 100% EtOAc) to obtain *tert*-butyl 8-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate as a semi-solid.
Yield: 98%; LCMS (Method D): Rt = 2.38 min, m/z = 646.4 $[M+H]^+$, 94.17%.

Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

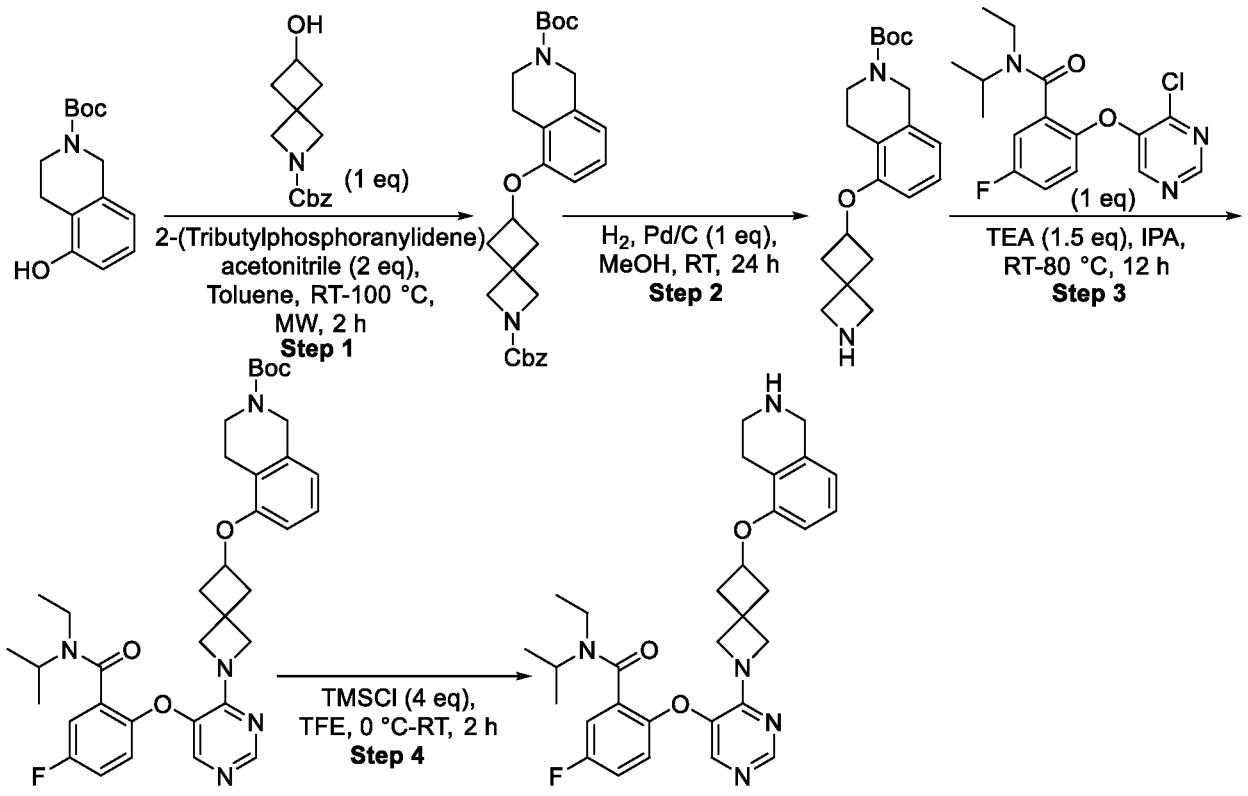


This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl 8-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-

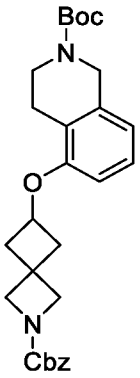
2(1H)-carboxylate. The crude was purified by Prep HPLC (Method AN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 23.51%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.24 (m, 1H), 7.78 - 7.63 (m, 1H), 7.34 - 7.20 (m, 2H), 7.11 - 6.92 (m, 2H), 6.65 (d, J = 7.6 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 4.66 - 4.57 (m, 1H), 4.37 - 4.05 (m, 4H), 3.82 - 3.64 (m, 3H), 3.44 - 3.35 (m, 1H), 3.26 - 3.09 (m, 1H), 2.89 (t, J = 5.8 Hz, 2H), 2.78 - 2.68 (m, 2H), 2.64 (t, J = 5.8 Hz, 2H), 2.27 - 2.12 (m, 2H), 1.22 - 0.96 (m, 9H), one proton merged with solvent peaks. LCMS (Method H): Rt = 1.31 min, m/z = 546.3 $[M+H]^+$; HPLC (Method A): Rt = 5.29 min, 96.82%.

Example 310. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 14)



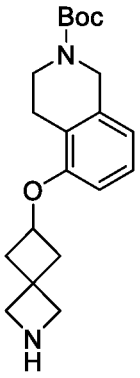
Step 1. tert-Butyl 5-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 309, step 1, starting with benzyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of *tert*-butyl 5-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate and 2 equivalents of 2-(tributylphosphoranylidene) acetonitrile were used. After completion, the reaction was quenched with water and extracted with EtOAc. The combined organic layer was dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to afford crude *tert*-butyl 5-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate as a liquid. This material was used without further purification.

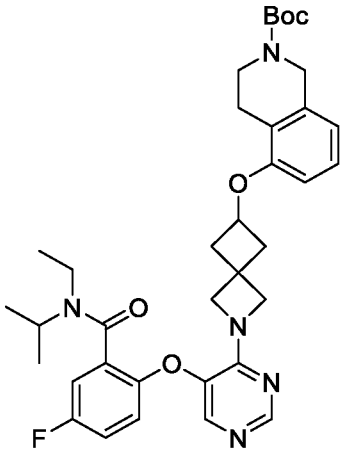
Yield: 56.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 - 7.29 (m, 5H), 7.10 (t, J = 7.9 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 5.03 - 5.01 (m, 2H), 4.65 - 4.57 (m, 1H), 4.45 (br s, 2H), 4.07 - 3.89 (m, 2H), 3.53 (t, J = 5.8 Hz, 2H), 2.76 - 2.66 (m, 2H), 2.60 (t, J = 5.9 Hz, 2H), 2.24 - 2.17 (m, 2H), 1.63 - 1.53 (m, 2H), 1.42 (s, 9H); LCMS (Method H): Rt = 2.55 min, m/z = 379.2 [M-100+H]$^+$, 91.93%.

Step 2. tert-Butyl 5-((2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



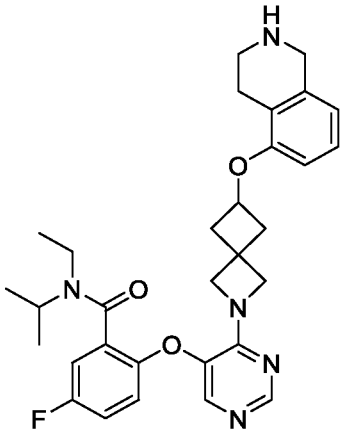
This compound was synthesized following the procedure described for the synthesis of Example 309, step 2, starting with 1 equivalent of *tert*-butyl 5-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl 5-((2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate as a semi-solid.
Yield: 92.0%; LCMS (Method H): Rt = 1.43 min, m/z = 345.1 $[M+H]^+$, 67.50%.

Step 3. tert-Butyl 5-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide , except that 1 equivalent of *tert*-butyl 5-((2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate and 1.5 equivalents of TEA were used. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 100% EtOAc) to obtain *tert*-butyl 5-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate as a semi-solid.
Yield: 33.3%; LCMS (Method H): Rt = 2.02 min, m/z = 646.4 $[M+H]^+$, 91.48%.

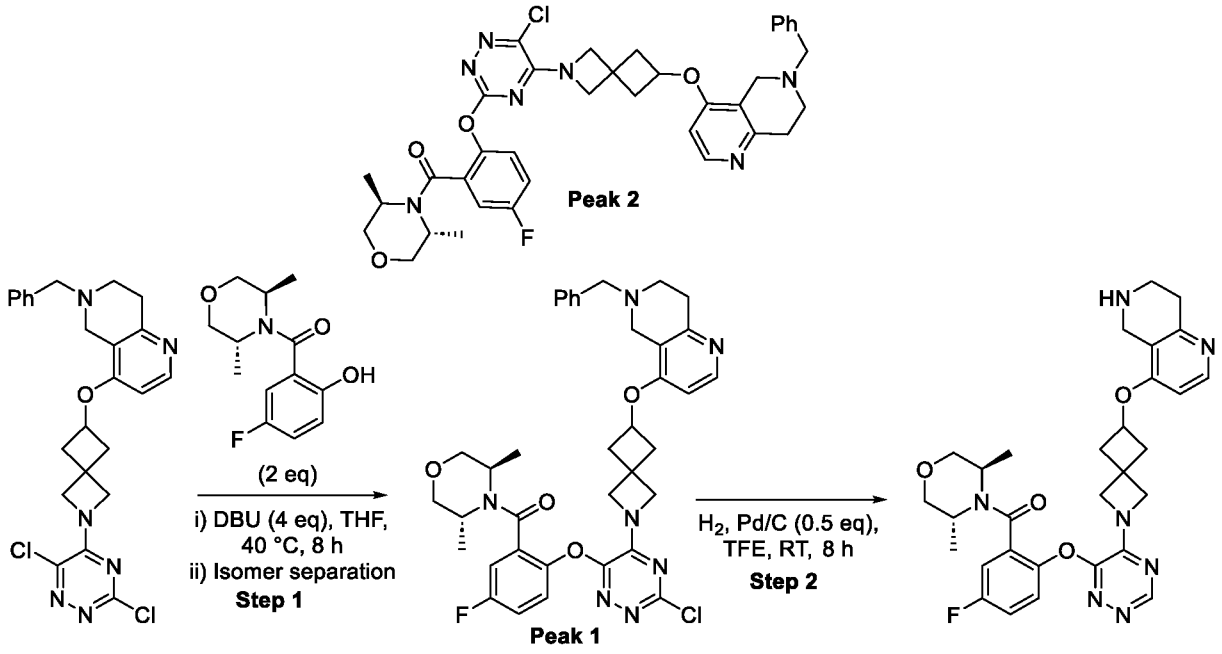
Step 4. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



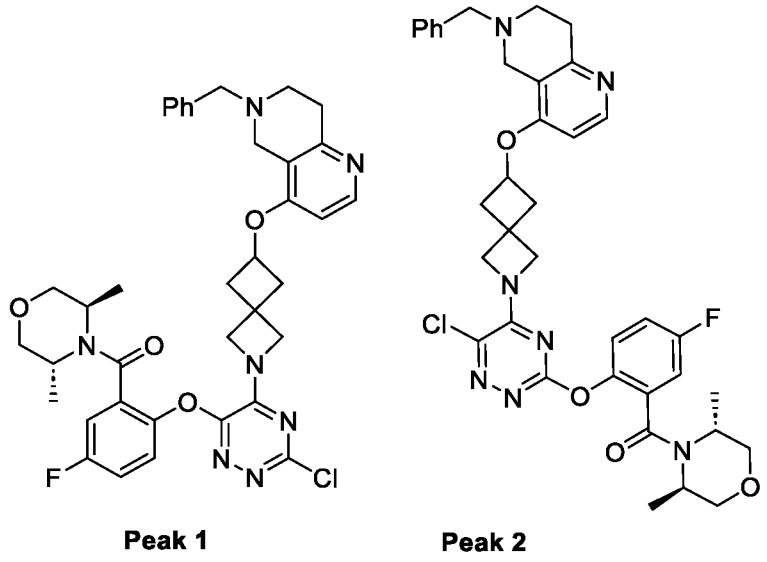
This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with *tert*-butyl 5-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate. The crude was purified by Prep HPLC (Method AN) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 58%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.20 (m, 2H), 7.11 - 6.95 (m, 2H), 6.61 - 6.53 (m, 2H), 4.66 - 4.57 (m, 1H), 4.48 - 4.05 (m, 4H), 3.78 (br s, 2H), 3.75 - 3.72 (m, 1H), 3.43 - 3.37 (m, 2H), 3.27 - 3.20 (m, 1H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.78 - 2.70 (m, 2H), 2.27 - 2.16 (m, 2H), 1.22 - 0.96 (m, 9H), two protons merged with solvent peaks; LCMS (Method D): Rt = 1.80 min, m/z = 546.2 $[M+H]^+$; HPLC (Method A): Rt = 5.23 min, 99.44%.

Example 311. ((3*R*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (Compound No. 343)



Step 1. (2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3R,5R)-3,5-dimethylmorpholino)methanone and (2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluorophenyl)((3R,5R)-3,5-dimethylmorpholino)methanone

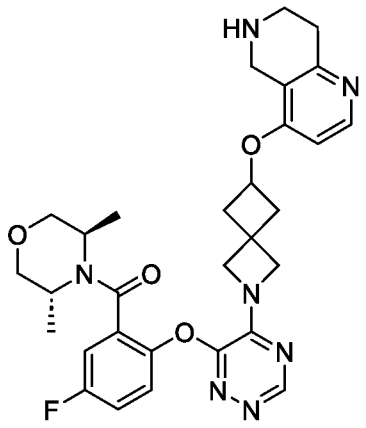


This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 2 equivalents

of ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain a mixture of regioisomers (3.5 g, LCMS purity: 96%). The regioisomers were separated by chiral Prep SFC (Method AP) to obtain (2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone as a solid. Yield: 30.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (t, J = 5.5 Hz, 1H), 7.53 - 7.20 (m, 8H), 6.68 (t, J = 4.9 Hz, 1H), 4.86 - 4.48 (m, 4H), 4.34 - 4.15 (m, 2H), 3.82 - 3.56 (m, 6H), 3.47 (s, 2H), 2.94 - 2.65 (m, 6H), 2.38 - 2.20 (m, 2H), 1.14 (br t, J = 6.4 Hz, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.20 min, m/z = 700.3 $[M+H]^+$, 82.29%.

Note: Peak 2 was not isolated.

Step 2. ((3R,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone



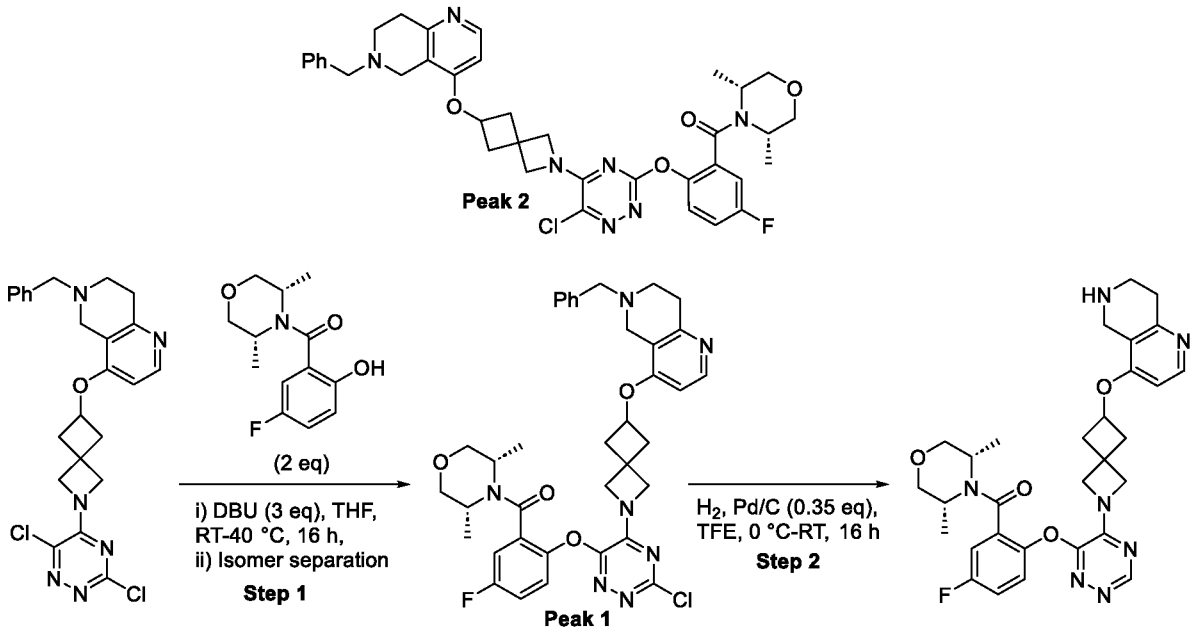
In a 100 mL round bottom flask, (2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone (1.5 g, 2.142 mmol) was added in TFE (20 mL). To this solution, Pd-C (1.140 g, 1.071 mmol) was added, and the reaction was stirred at RT for 1 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (3 x 30 mL). The filtrate was

concentrated under reduced pressure. The crude was purified by neutral alumina using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain crude ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (1.0 g, 75% yield, LCMS (Method G) : Rt = 1.32 min, m/z = 576.2 $[M+H]^+$, 92.51%).

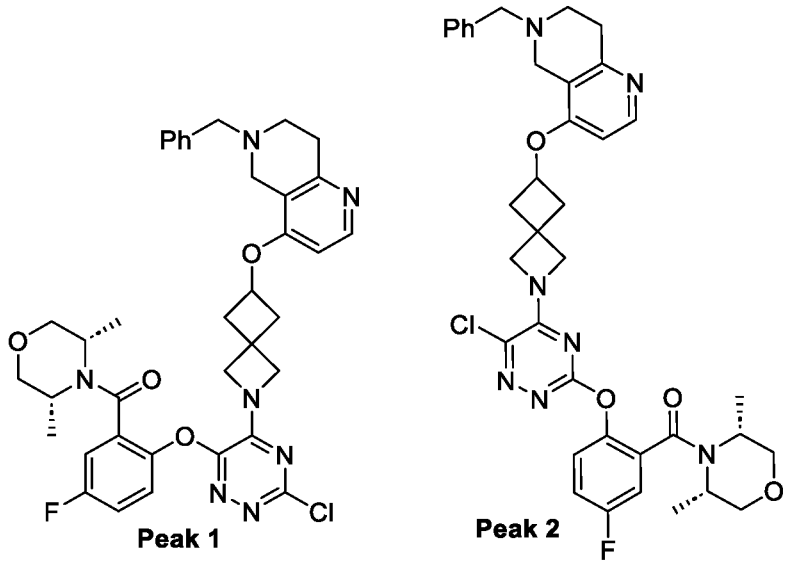
This crude compound (300 mg) was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (117 mg) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 8.18 (d, *J* = 5.5 Hz, 1H), 7.51 - 7.36 (m, 3H), 6.67 (br d, *J* = 5.5 Hz, 1H), 4.77 (quin, *J* = 6.6 Hz, 1H), 4.70 - 4.44 (m, 2H), 4.35 - 4.10 (m, 2H), 3.95 - 3.47 (m, 5H), 3.29 - 3.09 (m, 2H), 2.95 (br t, *J* = 5.4 Hz, 2H), 2.90 - 2.73 (m, 2H), 2.72 - 2.63 (m, 2H), 2.44 - 2.16 (m, 3H), 1.13 (br d, *J* = 3.9 Hz, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.32 min, m/z = 576.2 $[M+H]^+$; HPLC (Method G): Rt = 3.98 min, 99.24%.

Example 312. ((3*S*,5*R*)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (Compound No. 344)



Step 1. (2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3S,5R)-3,5-dimethylmorpholino)methanone and (2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluorophenyl)((3S,5R)-3,5-dimethylmorpholino)methanone



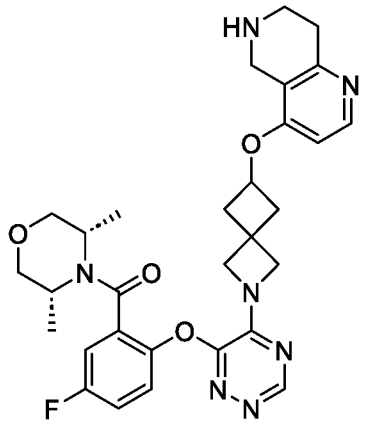
This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 2 equivalents of ((3*S*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-hydroxyphenyl)methanone, except that 3 equivalents of DBU was used. After work-up, the crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 15% MeOH in DCM) to obtain a mixture of regioisomers. The regioisomers were further purified by chiral Prep SFC (Method AH). The product fractions (peak 1) were concentrated under reduced pressure to obtain (2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone as a solid.

Yield: 37.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (t, J = 5.6 Hz, 1H), 7.52 - 7.43 (m, 2H), 7.42 - 7.24 (m, 6H), 6.68 (d, J = 5.6 Hz, 1H), 4.75 (quin, J = 6.5 Hz, 1H), 4.68 - 4.48 (m, 2H), 4.31 - 4.17 (m, 2H), 3.77 - 3.52 (m, 5H), 3.47 (s, 2H), 2.89 - 2.76 (m, 4H), 2.74 -

2.66 (m, 2H), 2.32 - 2.22 (m, 2H), 1.38 - 1.12 (m, 6H), three protons merged with solvent peaks; LCMS (Method G): Rt = 2.20 min, m/z = 700.3 $[M+H]^+$, 98.98%.

Note: Peak 2 was not isolated.

Step 2. ((3S,5R)-3,5-Dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone

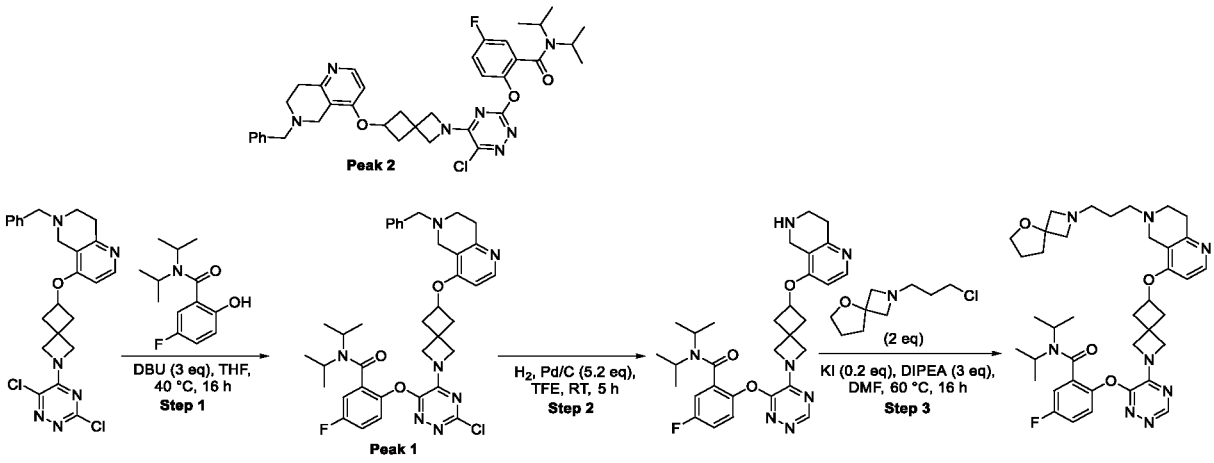


This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of (2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone, except that 0.35 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. Saturated sodium bicarbonate solution was added to the residue and the mixture was extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (0.9 g, 83% yield) as a solid. This material was used without further purification.

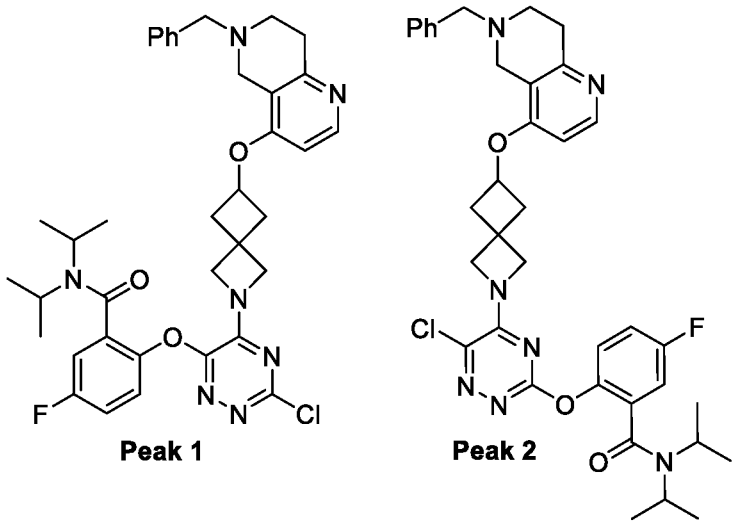
A portion of the crude compound (200 mg) was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced

pressure and lyophilized to obtain ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (101.22 mg) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.52 - 7.33 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 4.77 (quin, J = 6.4 Hz, 1H), 4.67 - 4.43 (m, 2H), 4.37 - 4.12 (m, 3H), 3.71 (br s, 2H), 3.66 - 3.42 (m, 3H), 2.95 (br s, 2H), 2.83 (br s, 2H), 2.68 (br s, 2H), 2.38 - 2.24 (m, 2H), 1.28 (br s, 6H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.49 min, m/z = 576.3 $[M+H]^+$; HPLC (Method G): Rt = 4.01 min, 99.92%.

Example 313. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (Compound No. 345)



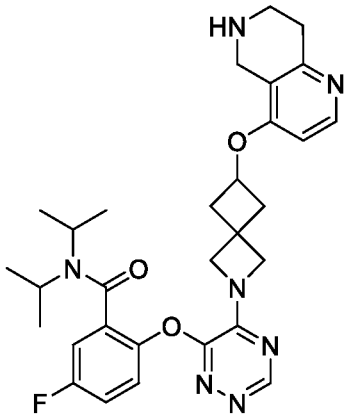
Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 2 equivalents of 5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide, except that 3 equivalents of DBU was used. The crude was purified by silica gel column chromatography using MeOH in DCM (product eluted at 15% MeOH in DCM) to obtain 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide and the other regioisomer (2.5 g, 38.5% yield) as a solid. The mixture of regioisomers was purified by achiral Prep SFC (Method AR) to obtain peak 1, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide as a solid.
Yield: 47.5% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 – 8.17 (m, 1H), 7.46 – 7.40 (m, 1H), 7.38 -7.21 (m, 7H), 6.66 (d, J = 6 Hz, 1H), 4.79 – 4.52 (m, 3H), 4.30 – 4.11 (m, 1H), 3.71 – 3.52 (m, 2H), 3.59 – 3.40 (m, 4H), 2.73 – 2.52 (m, 6H), 2.33 – 2.14 (m, 2H), 1.47 - 1.36 (m, 3H), 1.34 – 1.20 (m, 3H), 1.07 (br s, 3H), 0.72 (br s, 3H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.22 min, m/z = 686.2 $[M+H]^+$; HPLC (Method G): Rt = 7.27 min, 97.89%.

Note: Peak 2 was not isolated.

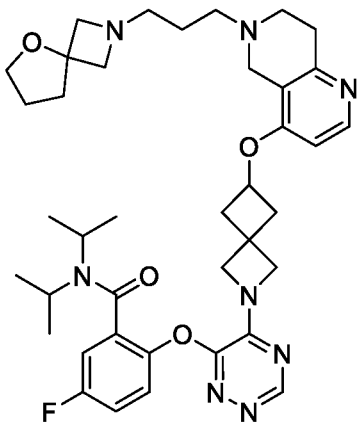
Step 2. 5-Fluoro-N,N-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide, except that 5.2 equivalents of Pd-C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure to obtain crude 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a sticky solid. This material was used without further purification.

Yield: Quantitative yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.44 (dd, J = 4.6, 8.8 Hz, 1H), 7.38 - 7.24 (m, 2H), 6.66 (d, J = 5.6 Hz, 1H), 4.77 (quin, J = 6.5 Hz, 1H), 4.71 - 4.48 (m, 2H), 4.31 - 4.07 (m, 2H), 3.71 (s, 2H), 3.61 - 3.51 (m, 1H), 3.50 - 3.40 (m, 1H), 2.95 (br t, J = 5.8 Hz, 2H), 2.88 - 2.73 (m, 2H), 2.71 - 2.65 (m, 3H), 2.33 - 2.19 (m, 2H), 1.42 (br s, 3H), 1.34 - 1.21 (m, 3H), 1.07 (br d, J = 6.4 Hz, 3H), 0.63 (br d, J = 6.4 Hz, 3H); LCMS (Method G): Rt = 1.46 min, m/z = 562.2 $[M+H]^+$, 85.21%.

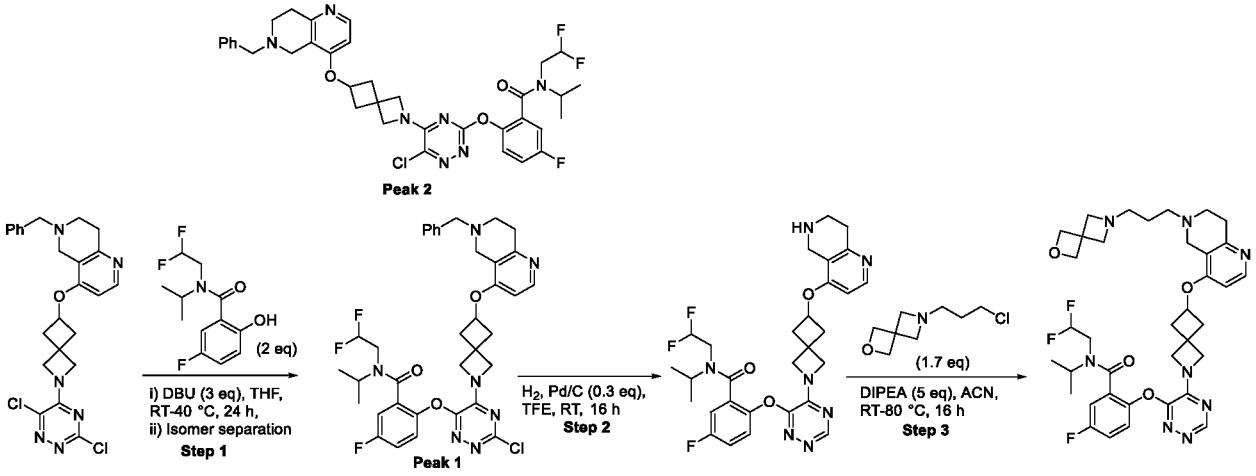
Step 3. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N,N-diisopropylbenzamide



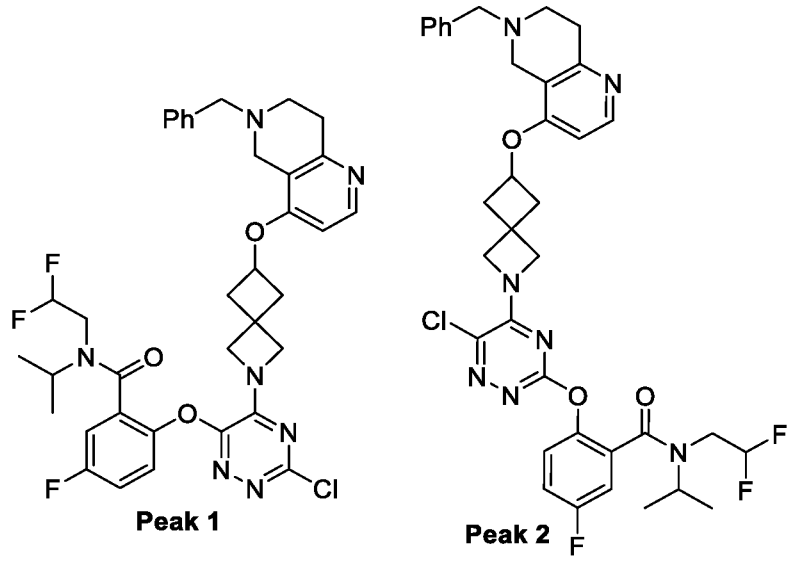
This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 2 equivalents of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane and 1 equivalent of 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 0.2 equivalent of KI was used. The reaction was stirred at 60 °C. After completion, the reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide as a solid.

Yield: 17.83%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.44 (dd, J = 4.6, 8.9 Hz, 1H), 7.38 - 7.25 (m, 2H), 6.68 (d, J = 5.6 Hz, 1H), 4.84 - 4.74 (m, 1H), 4.72 - 4.47 (m, 2H), 4.31 - 4.04 (m, 2H), 3.65 (t, J = 6.7 Hz, 2H), 3.61 - 3.50 (m, 1H), 3.50 - 3.43 (m, 1H), 3.40 (s, 2H), 3.29 - 3.22 (m, 2H), 2.92 - 2.73 (m, 7H), 2.70 - 2.63 (m, 3H), 2.44 - 2.33 (m, 3H), 2.02 - 1.95 (m, 2H), 1.80 (quin, J = 6.9 Hz, 2H), 1.57 - 1.46 (m, 2H), 1.42 (br d, J = 4.0 Hz, 3H), 1.29 (br d, J = 6.0 Hz, 3H), 1.07 (br d, J = 6.4 Hz, 3H), 0.64 (br d, J = 6.3 Hz, 3H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.76 min, m/z = 715.3 $[M+H]^+$; HPLC (Method G): Rt = 5.07 min, 97.22%.

Example 314. 2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 346)



Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



Step 1 was performed following the same procedure in two batches.

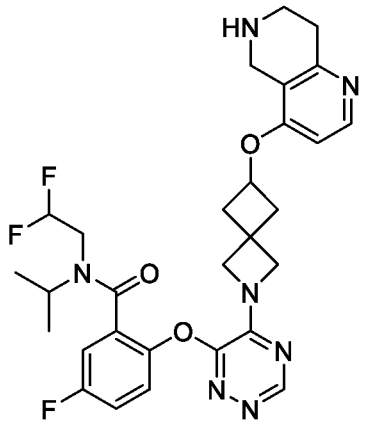
This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 2 equivalents

of *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 3 equivalents of DBU was used. After work-up, the crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to obtain a mixture of regioisomers. The products from both batches were mixed and purified by chiral Prep SFC (Method AJ) to obtain pure regioisomers. The product fractions (peak 1) were concentrated under reduced pressure to obtain 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Combined yield: 32.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (t, J = 5.3 Hz, 1H), 7.52 - 7.19 (m, 8H), 6.71 - 6.64 (m, 1H), 6.39 - 6.01 (m, 1H), 4.80 - 4.68 (m, 1H), 4.66 - 4.48 (m, 2H), 4.29 - 4.13 (m, 2H), 3.81 - 3.52 (m, 5H), 3.47 (s, 2H), 2.85 - 2.78 (m, 4H), 2.74 - 2.66 (m, 2H), 2.33 - 2.22 (m, 2H), 1.22 - 0.72 (m, 6H); LCMS (Method G): Rt = 2.14 min, m/z = 708.1 $[M+H]^+$; HPLC (Method G): Rt = 6.99 min, 99.88%.

Note: Peak 2 was not isolated.

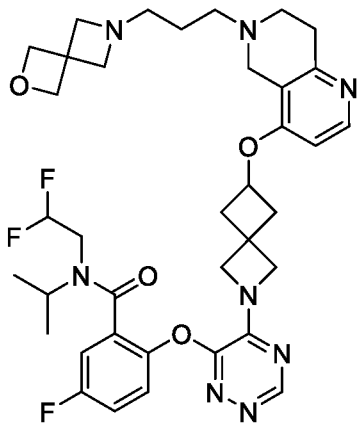
Step 2. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamid, except that 0.3 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed

with 2,2,2-trifluoroethanol. The filtrate was concentrated under reduced pressure. Saturated sodium bicarbonate was added to the crude and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to afford crude *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (10.9 g, 85% yield) as a solid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.50 - 7.37 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 6.35 - 6.00 (m, 1H), 4.82 - 4.69 (m, 1H), 4.64 - 4.42 (m, 2H), 4.28 - 4.10 (m, 2H), 3.93 - 3.66 (m, 4H), 3.63 - 3.46 (m, 1H), 2.97 (br t, J = 5.8 Hz, 2H), 2.89 - 2.78 (m, 3H), 2.69 (br t, J = 5.6 Hz, 2H), 2.37 - 2.25 (m, 2H), 1.19 - 0.64 (m, 6H); LCMS (Method G): Rt = 1.44 min, m/z = 584.2 $[M+H]^+$; HPLC (Method G): Rt = 4.48 min, 95.86%.

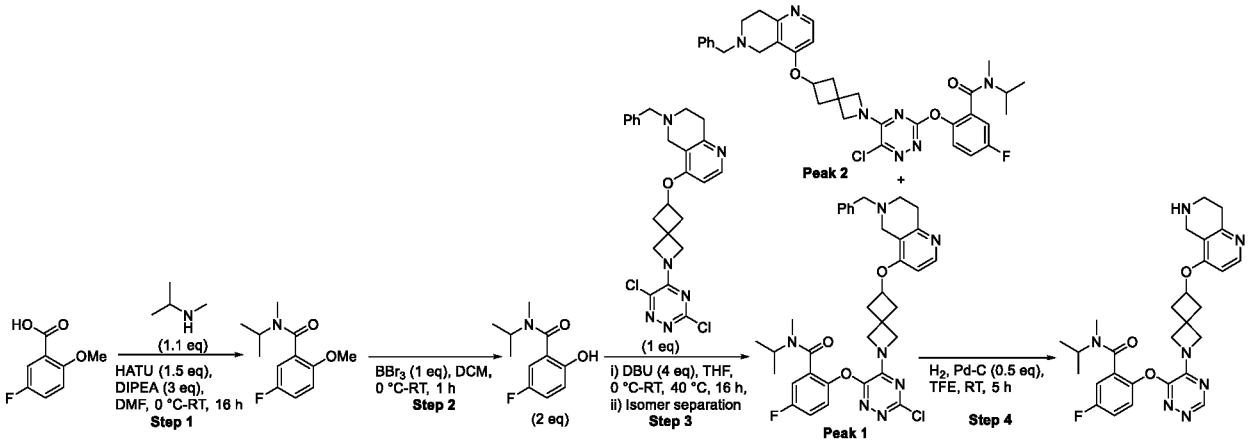
Step 3. 2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



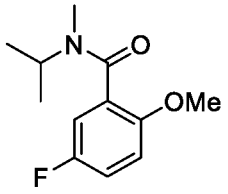
This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 1.7 equivalents of 6-(3-chloropropyl)-2-oxa-6-azaspiro[3.3]heptane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 80 °C. The reaction was diluted saturated aqueous sodium bicarbonate solution and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The

crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (60 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AM). The product fractions were concentrated under reduced pressure and lyophilized to afford 2-((5-(6-((6-(3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid. Yield: 12.01%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.51 - 7.37 (m, 3H), 6.68 (d, J = 5.8 Hz, 1H), 6.37 - 5.98 (m, 1H), 4.83 - 4.72 (m, 1H), 4.63 - 4.44 (m, 6H), 4.28 - 4.11 (m, 2H), 3.83 - 3.65 (m, 2H), 3.64 - 3.47 (m, 1H), 3.39 (br s, 2H), 3.21 (br s, 4H), 2.87 - 2.77 (m, 4H), 2.67 - 2.61 (m, 2H), 2.48 - 2.41 (m, 2H), 2.36 - 2.25 (m, 4H), 1.46 (br s, 2H), 1.22 - 0.67 (m, 6H); LCMS (Method G): Rt = 1.57 min, m/z = 723.2 $[M+H]^+$; HPLC (Method G): Rt = 4.69 min, 99.71%.

Example 315. 5-Fluoro-*N*-isopropyl-*N*-methyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 347)



Step 1. 5-Fluoro-N-isopropyl-2-methoxy-N-methylbenzamide



Step 1 was performed following the same procedure in two batches.

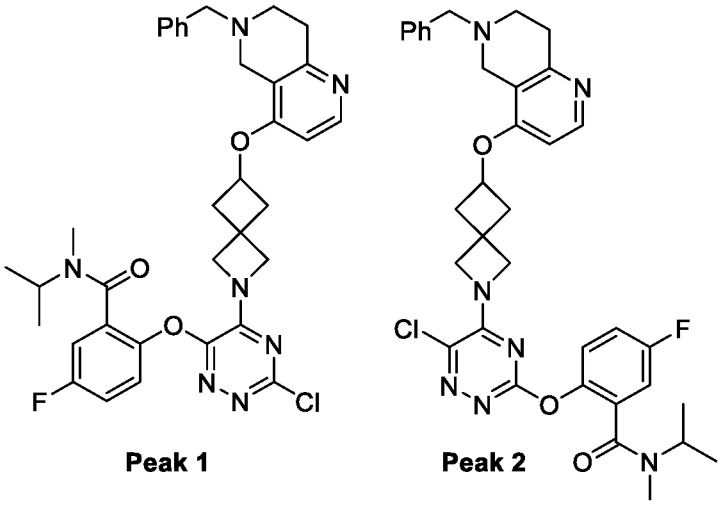
This compound was synthesized following the procedure described for the synthesis of Example 3, step 1, starting with 1 equivalent of 5-fluoro-2-methoxybenzoic acid, except that 3 equivalents of DIPEA and 1.1 equivalents of *N*-methylpropan-2-amine were used. After work-up, the crude compound was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 5% MeOH in DCM) to afford 5-fluoro-*N*-isopropyl-2-methoxy-*N*-methylbenzamide as a semi-solid.
Yield: 38.2%; LCMS (Method B): Rt = 1.66 min, m/z = 226.3 $[M+H]^+$, 97.99%.

Step 2. 5-Fluoro-2-hydroxy-N-isopropyl-N-methylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 3, step 2, starting with 1 equivalent of 5-fluoro-*N*-isopropyl-2-methoxy-*N*-methylbenzamide. After work-up, the crude compound was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 40-50% EtOAc in hexane) to obtain 5-fluoro-2-hydroxy-*N*-isopropyl-*N*-methylbenzamide as a solid.
Yield: 70.4%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 7.10 - 7.04 (m, 1H), 7.01 - 6.95 (m, 2H), 4.65 - 4.62 (m, 1H), 2.99 (s, 3H), 1.27 (d, *J* = 6.6 Hz, 6H); LCMS (Method B): Rt = 1.49 min, m/z = 212.2 $[M+H]^+$, 83.65%.

Step 3. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-methylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-N-isopropyl-N-methylbenzamide



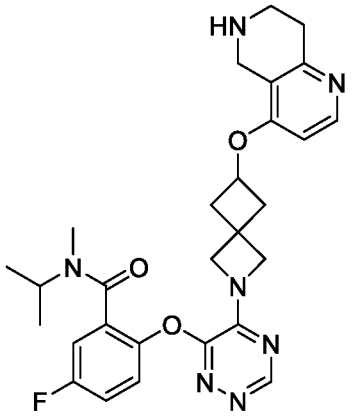
This compound was synthesized following the procedure described for the synthesis of Example 3, step 3, starting with 2 equivalents of 5-fluoro-2-hydroxy-*N*-isopropyl-*N*-methylbenzamide and 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine, except that 3 equivalent of DBU was used. After work-up, the crude compound was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 5-8% MeOH in DCM), then by chiral Prep SFC (Method V) to obtain both isomers.

Peak 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide (750 mg, 10.68% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23-8.18 (m, 1H), 7.51 - 7.41 (m, 1H), 7.40 - 7.32 (m, 6H), 7.31 - 7.23 (m, 1H), 6.69 - 6.65 (m, 1H), 4.79 - 4.70 (m, 1H), 4.69 - 4.49 (m, 2H), 4.30 - 4.15 (m, 2H), 3.73 - 3.64 (m, 2H), 3.47 (br s, 2H), 2.86 - 2.75 (m, 6H), 2.74 - 2.66 (m, 2H), 2.60 - 2.56 (m, 2H), 2.35 - 2.22 (m, 2H), 1.06-1.03 (m, 3H), 1.02 - 0.97 (m, 3H); LCMS (Method G): Rt = 2.05 min, m/z = 658.1 $[M+H]^+$, 88.74%.

Peak 2. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide (480 mg, 7.50% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, J = 5.6 Hz, 1H), 7.38 - 7.35 (m, 5H), 7.34 - 7.25 (m, 3H), 6.67 (d, J = 5.6 Hz, 1H), 4.78 - 4.67 (m, 2H), 4.69 - 4.53 (m, 2H), 4.14 - 3.98 (m, 2H), 3.82 - 3.72 (m, 1H), 3.69 (br s, 2H),

3.46 (br s, 2H), 2.85 - 2.73 (m, 6H), 2.64 - 2.59 (m, 2H), 2.30 - 2.22 (m, 2H), 1.09 - 1.02 (m, 3H), 1.02 - 0.89 (m, 3H); LCMS (Method G): Rt = 2.05 min, m/z = 658.1 $[M+H]^+$, 97.33%.

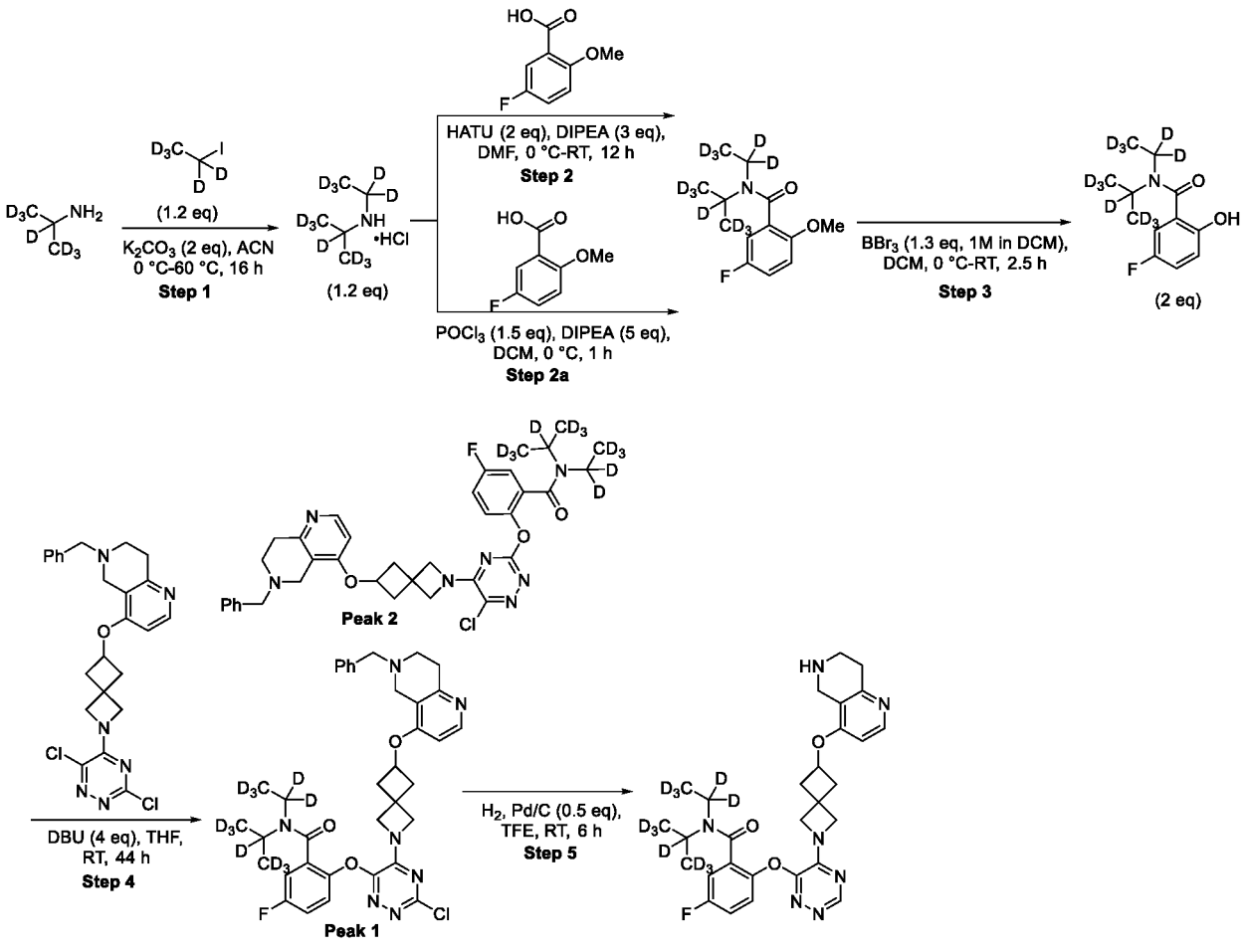
Step 4. 5-Fluoro-N-isopropyl-N-methyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



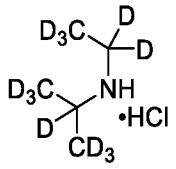
This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 5-fluoro-*N*-isopropyl-*N*-methyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 54.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ ; 8.46 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.39 - 7.30 (m, 2H), 6.67 (d, J = 5.7 Hz, 1H), 4.79 - 4.74 (m, 1H), 4.64 - 4.51 (m, 2H), 4.26 - 4.13 (m, 2H), 3.71 (br s, 2H), 2.96 (t, J = 5.6 Hz, 2H), 2.87 - 2.75 (m, 4H), 2.69 (t, J = 5.4 Hz, 2H), 2.57 (s, 3H), 2.36 - 2.28 (m, 2H), 1.16 - 0.71 (m, 6H); LCMS (Method G): Rt = 1.49 min, m/z = 534.2 $[M+H]^+$; HPLC (Method G): Rt = 4.04 min, 99.54%.

Example 316. ***N*-(Ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide** (Compound No. 348)



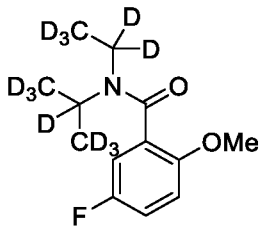
Step 1. N-(Ethyl-d_5)propan-d_7-2-amine hydrochloride



In a 10 mL sealed tube, to a solution of propan-d_7-2-amine (200 mg, 3.02 mmol) in ACN (3 mL), K_2CO_3 (836 mg, 6.05 mmol) and 1-iodoethane-1,1,2,2,2-d_5 (730 mg, 4.53 mmol) were added at 0 °C. The reaction was stirred at 60 °C for 12 h. The reaction progress was monitored by crude NMR. After completion, the reaction was diluted with EtOAc (5 mL) and filtered. The filtrate was cooled to 0 °C, 2 mL HCl (4.0 M dioxane) was added, and the

mixture was stirred for 10 min. The mixture was concentrated under reduced pressure to obtain crude *N*-(ethyl-d_5)propan-d_7-2-amine hydrochloride (500 mg, quantitative yield) as a sticky liquid. This material was used without further purification. LCMS-ELSD (Method G): Rt = 0.52 min, m/z = 100.3 $[M+H]^+$, 96.12%.

Step 2. N-(Ethyl-d_5)-5-fluoro-2-methoxy-N-(propan-2-yl-d_7)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 3, step 1, starting with 5-fluoro-2-methoxybenzoic acid, except that 1.2 equivalents of *N*-(ethyl-d_5)propan-d_7-2-amine hydrochloride, 2 equivalents of HATU, and 3 equivalents of DIPEA were used. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 25% EtOAc in hexane) to obtain *N*-(ethyl-d_5)-5-fluoro-2-methoxy-*N*-(propan-2-yl-d_7)benzamide as a solid.
Yield: 22.56%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.02 (ddd, *J* = 3.1, 8.1, 8.9 Hz, 1H), 6.97 - 6.91 (m, 1H), 6.85 (dd, *J* = 4.1, 9.0 Hz, 1H), 3.82 (s, 3H); LCMS (Method G): Rt = 2.12 min, m/z = 252.2 $[M+H]^+$, 98.32%.

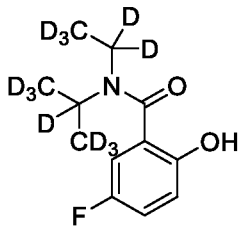
Step 2a. N-(Ethyl-d_5)-5-fluoro-2-methoxy-N-(propan-2-yl-d_7)benzamide

This reaction was performed following the same procedure in two batches (900 mg and 300 mg).

In a dried, 100 mL round bottom flask under a nitrogen atmosphere, 5-fluoro-2-methoxybenzoic acid (900 mg, 5.29 mmol) and *N*-(ethyl-d_5)propan-d_7-2-amine hydrochloride (861 mg, 6.35 mmol) were added in DCM (15 mL). To this reaction mixture, DIPEA (4.62 mL, 26.4 mmol) and $POCl_3$ (0.740 mL, 7.93 mmol, in 2 mL DCM) were added at 0 °C. The reaction was stirred at the same temperature for 1 h. The reaction was monitored by TLC (40% EtOAc in hexane). After completion, water (10 mL) was added to the reaction, and the

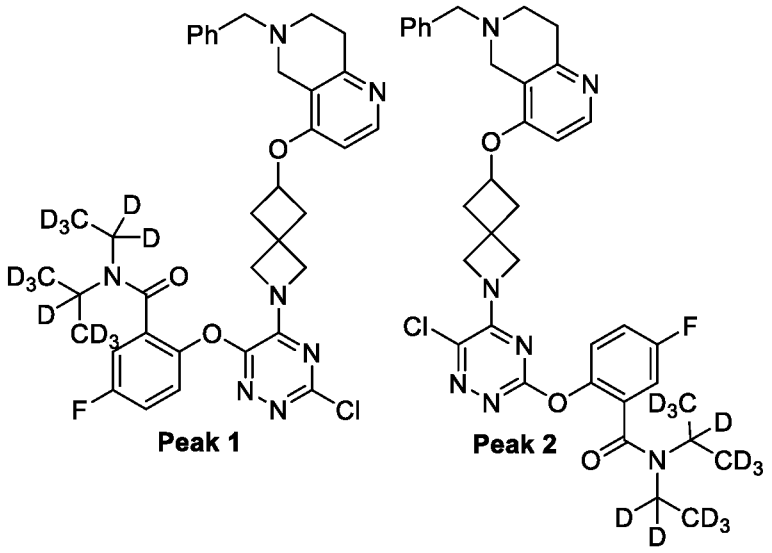
mixture was extracted with DCM (2 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product from both batches were combined and purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 20% EtOAc in hexane) to obtain *N*-(ethyl-d_5)-5-fluoro-2-methoxy-*N*-(propan-2-yl-d_7)benzamide (700 mg, 42.8% combined yield) as a solid. LCMS (Method G): Rt = 1.88 min, m/z = 252.2 $[M+H]^+$, 81.32%.

Step 3. N-(Ethyl-d_5)-5-fluoro-2-hydroxy-N-(propan-2-yl-d_7)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 3, step 2, starting with 1 equivalent of *N*-(ethyl-d_5)-5-fluoro-2-methoxy-*N*-(propan-2-yl-d_7)benzamide, except that 1.3 equivalents of BBr_3 was used. The reaction progress was monitored by TLC (40% EtOAc in hexane). After completion, water was added to the reaction at 0 °C, and the mixture was extracted with DCM. The combined organic layer was washed with saturated $NaHCO_3$, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 25% EtOAc in hexane) to obtain *N*-(ethyl-d_5)-5-fluoro-2-hydroxy-*N*-(propan-2-yl-d_7)benzamide as a solid. Yield: 55.1%; LCMS (Method G): Rt = 1.60 min, m/z = 238.2 $[M+H]^+$, 66.89%.

Step 4. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(ethyl-d_5)-5-fluoro-N-(propan-2-yl-d_7)benzamide

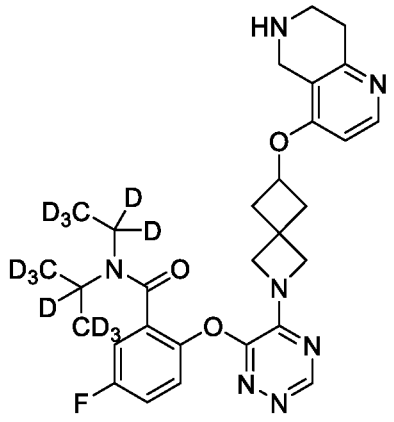


This reaction was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Example 3, step 3, starting with 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 2 equivalents of *N*-(ethyl-d_5)-5-fluoro-2-hydroxy-*N*-(propan-2-yl-d_7)benzamide, except that 4 equivalents of DBU was used. The crude from both batches were combined and purified by silica gel column chromatography using MeOH in DCM (product was eluted at 13% MeOH in DCM) to obtain a mixture of regioisomers (650 mg, LCMS (Method G): Rt = 2.11 min, m/z = 684.3 $[M+H]^+$, 79.63%). The mixture was further purified by achiral Prep SFC (Method F) to obtain peak-1, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)benzamide as a solid.

Combined yield: 17.62%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 - 8.15 (m, 1H), 7.50 - 7.22 (m, 8H), 6.68 (d, *J* = 5.7 Hz, 1H), 4.75 (quin, *J* = 6.6 Hz, 1H), 4.69 - 4.62 (m, 1H), 4.60 - 4.53 (m, 1H), 4.32 - 4.12 (m, 2H), 3.74 - 3.63 (m, 2H), 3.47 (s, 2H), 2.88 - 2.75 (m, 4H), 2.75 - 2.66 (m, 2H), 2.35 - 2.21 (m, 2H); LCMS (Method G): Rt = 2.18 min, m/z = 684.3 $[M+H]^+$, 93.05%.

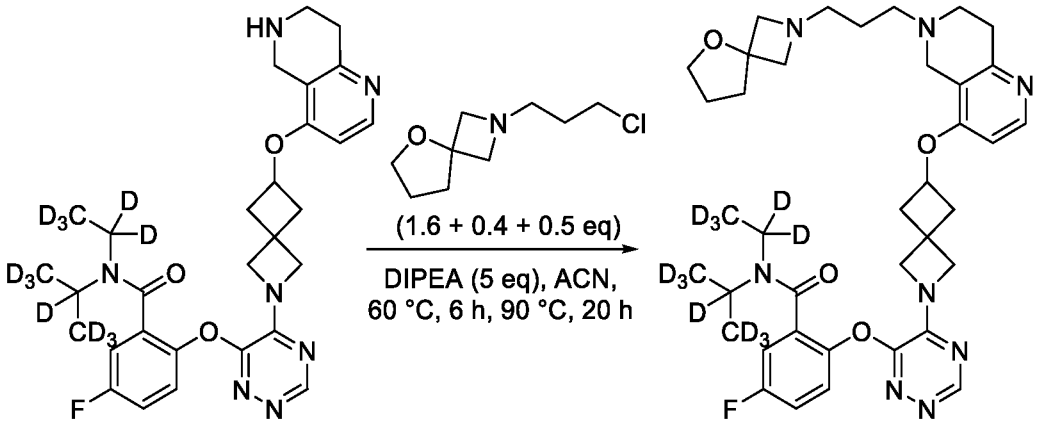
Step 5. N-(Ethyl-d_5)-5-fluoro-N-(propan-2-yl-d_7)-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)benzamide. The reaction progress was monitored by LCMS (Method G). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

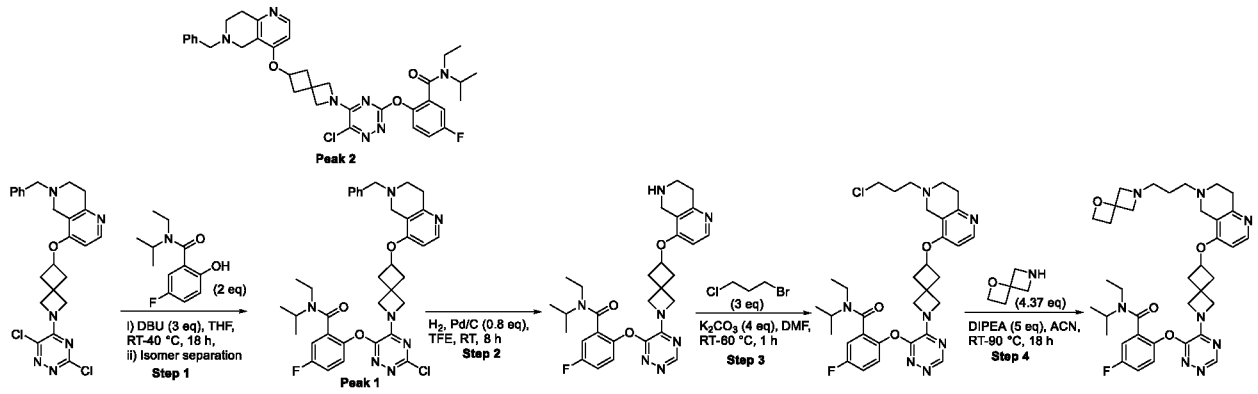
Yield: 53.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.18 (d, *J* = 5.5 Hz, 1H), 7.49 - 7.30 (m, 3H), 6.67 (d, *J* = 5.7 Hz, 1H), 4.77 (quin, *J* = 6.6 Hz, 1H), 4.69 - 4.43 (m, 2H), 4.29 - 4.07 (m, 2H), 3.71 (s, 2H), 2.95 (br t, *J* = 5.7 Hz, 2H), 2.88 - 2.77 (m, 2H), 2.68 (br t, *J* = 5.1 Hz, 2H), 2.34 - 2.25 (m, 2H), one proton is merged with solvent peaks; LCMS (Method D): Rt = 1.41 min, m/z = 560.3 $[M+H]^+$; HPLC (Method G): Rt = 4.21 min, 99.31%.

Example 317. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)benzamide (Compound No. 349)

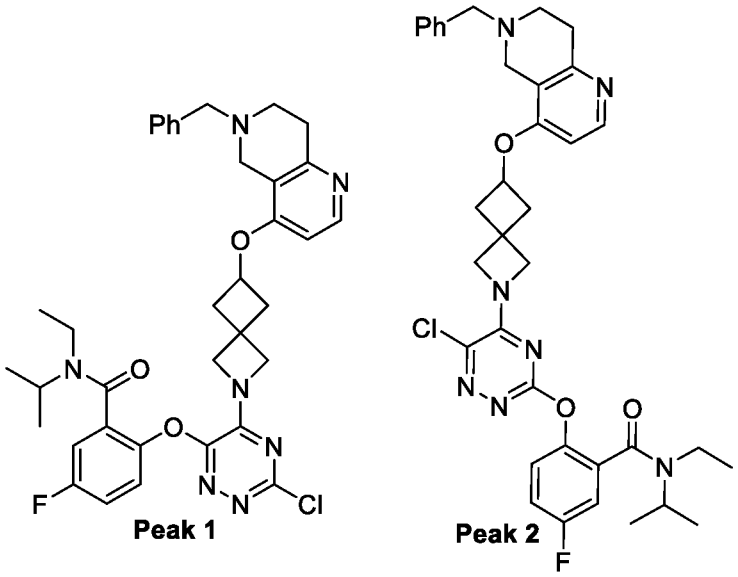


In an 8 mL pressure vial, to a solution of *N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (30 mg, 0.054 mmol) and 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (16.27 mg, 0.086 mmol) in ACN (1.5 mL), DIPEA (0.047 mL, 0.268 mmol) was added at RT. The reaction was stirred at 60 °C for 6 h. The starting material was not consumed. Therefore, another lot of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (4.07 mg, 0.021 mmol) was added and the reaction was continued at 90 °C for 12 h. The starting material was still not consumed. Therefore, a third lot of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (5.08 mg, 0.027 mmol) was added, and the reaction was continued at 90 °C for 8 h. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(ethyl-d_5)-5-fluoro-*N*-(propan-2-yl-d_7)benzamide (10 mg, 24.95% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, *J* = 5.5 Hz, 1H), 7.50 - 7.30 (m, 3H), 6.68 (d, *J* = 5.7 Hz, 1H), 4.79 (quin, *J* = 6.6 Hz, 1H), 4.70 - 4.46 (m, 2H), 4.33 - 4.07 (m, 2H), 3.73 - 3.59 (m, 3H), 3.40 (s, 2H), 3.28 - 3.21 (m, 2H), 2.95 - 2.74 (m, 7H), 2.71 - 2.61 (m, 2H), 2.46 - 2.27 (m, 6H), 2.02 - 1.93 (m, 2H), 1.80 (quin, *J* = 6.9 Hz, 2H); LCMS (Method B): Rt = 0.99 min, m/z = 713.4 $[M+H]^+$; HPLC (Method G): Rt = 4.73 min, 95.34%.

Example 318. 2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 335)



Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



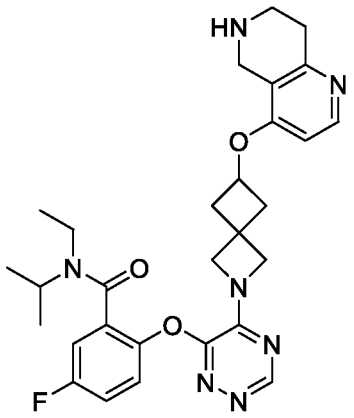
This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 2 equivalents of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 3 equivalents of DBU were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (products eluted at 10% MeOH in DCM) to obtain a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and the other regioisomer. The regioisomers were purified by achiral Prep SFC (Method I) to obtain peak 1, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 52.0%; LCMS (Method G): Rt = 2.33 min, m/z = 672.5 $[M+H]^+$, 93.85%.

Note: Peak 2 was not isolated.

Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



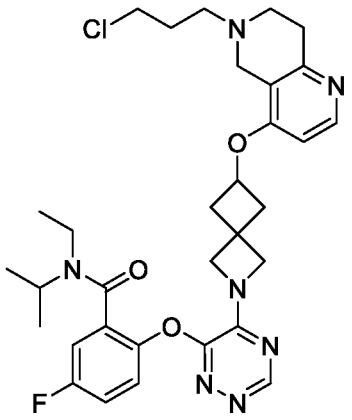
This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.8 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol. The filtrate was concentrated under reduced pressure to obtain crude *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid. This material was used without further purification

Yield: 91%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.33 (d, J = 5.5 Hz, 1H), 7.50 - 7.31 (m, 3H), 6.83 (d, J = 5.7 Hz, 1H), 4.86 (quin, J = 6.5 Hz, 1H), 4.69 - 4.49 (m, 2H), 4.31 - 4.14 (m, 2H), 4.09 (s, 2H), 3.68 - 3.57 (m, 1H), 3.44 - 3.37 (m, 3H), 3.14 - 2.94 (m, 3H), 2.85 (br s, 2H), 2.39 - 2.25 (m, 2H), 1.15 - 0.64 (m, 9H), one proton merged with solvent

peaks; LCMS (Method B): Rt = 0.99 min, m/z = 548.3 $[M+H]^+$, 96.47%. This material was used without further purification.

Note: In the ^{1}HNMR, 2,2,2-triflouroethanol impurity was observed. Therefore, the crude product was washed with Aq. $NaHCO_3$ solution and extracted with 10% MeOH in DCM.

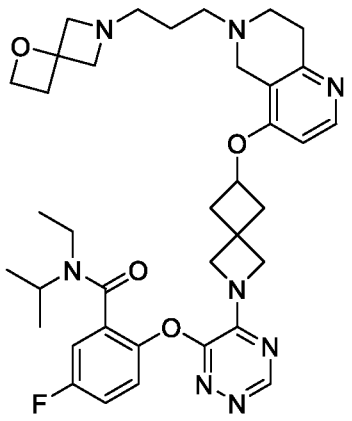
Step 3. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalents of 1-bromo-3-chloropropane, except that 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was used. The reaction was stirred in a pressure vial. After work up, the crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 37.7%; LCMS (Method G): Rt = 1.96 min, m/z = 624.5 $[M+H]^+$, 96.20%.

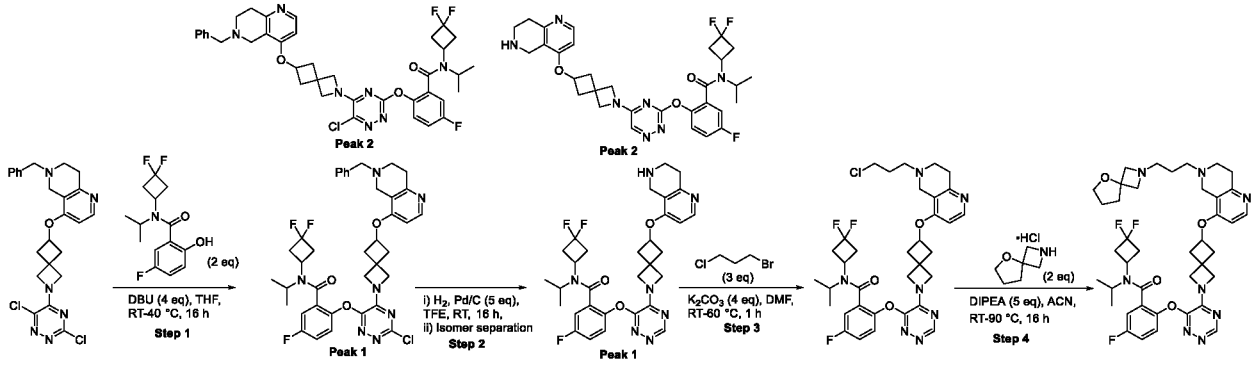
Step 4. 2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



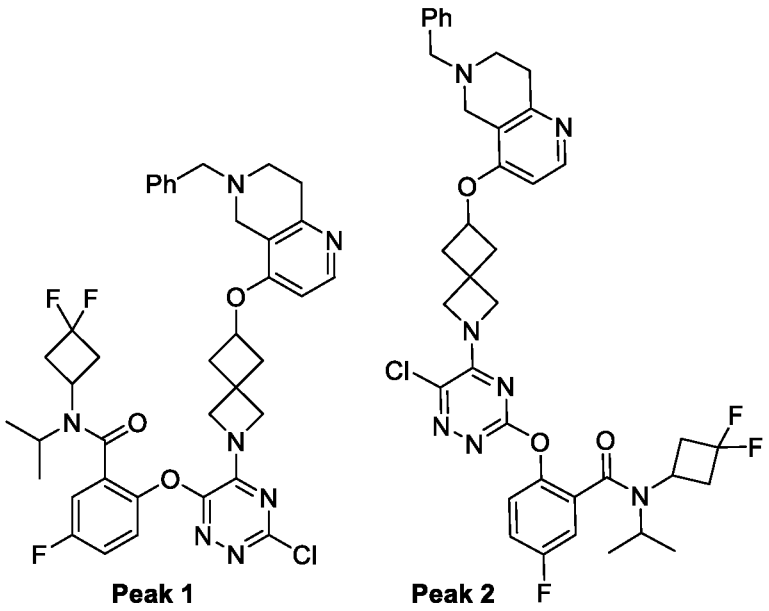
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent (2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 1.5 equivalents of 1-oxa-6-azaspiro[3.3]heptane. The reaction was stirred at 90 °C in a pressure vial. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method V). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(1-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 27.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.48 - 7.32 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.67 - 4.47 (m, 2H), 4.36 (t, J = 7.5 Hz, 2H), 4.32 - 4.12 (m, 2H), 3.68 - 3.57 (m, 1H), 3.49 (br d, J = 6.2 Hz, 2H), 3.40 (s, 2H), 3.16 - 2.93 (m, 4H), 2.89 - 2.76 (m, 5H), 2.73 (br t, J = 7.4 Hz, 2H), 2.68 - 2.62 (m, 2H), 2.46 - 2.26 (m, 4H), 1.48 (br s, 2H), 1.16 - 0.67 (m, 9H), one protons merged with solvent peaks; LCMS (Method G): Rt = 1.68 min, m/z = 687.6 $[M+H]^+$; HPLC (Method A): Rt = 4.68 min, 99.24%.

Example 319. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 350)



Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

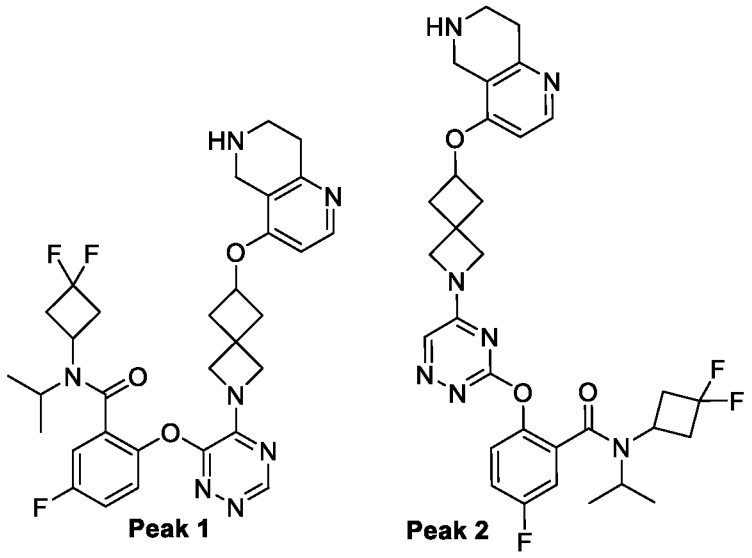


This compound was synthesized following the procedure described for the synthesis of Example 8, step 2, starting with 2 equivalents of *N*-(3,3-difluorocyclobutyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 1 equivalent of 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 4 equivalents of DBU were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted with 5-10% MeOH in DCM) to obtain a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and the other regioisomer as solids. The mixture of regioisomers were used without further purification.

Yield: 14.40%; LCMS (Method G): Rt = 2.46 min, m/z = 734.5 $[M+H]^+$, 92.01%.

Step 2. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide



To a stirred solution of a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (2 g, 2.72 mmol) in TFE (40 mL), dry Pd/C (1.449 g, 13.62 mmol) was added at RT. The reaction was continued under a hydrogen atmosphere (balloon pressure) at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 60 mL). The filtrate was concentrated under reduced pressure to afford a crude mixture of regioisomers, *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and the other regioisomer (1.7 g, 91 % yield) as solids. LCMS (Method G): Peak 1: Rt = 1.72 min, m/z = 610.5 $[M+H]^+$, 32.99%; Peak 2: Rt = 1.76 min, m/z = 610.5 $[M+H]^+$, 56.27%.

The mixture of regioisomers was purified by achiral Prep SFC (Method M) to obtain both regioisomers.

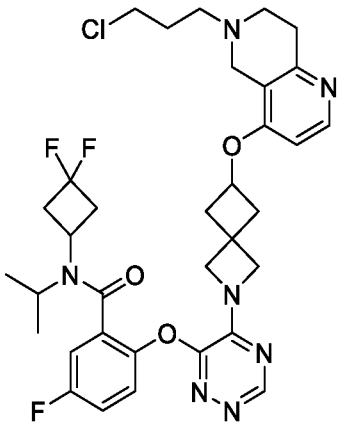
Peak 1. *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 28.8%; LCMS (Method G): Rt = 1.62 min, m/z = 610.1 $[M+H]^+$, 63.69%.

Peak 2: *N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide as a solid.

Yield: 27.6%; LCMS (Method G): Rt = 1.65 min, m/z = 610.1 $[M+H]^+$, 93.85%.

Step 3. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

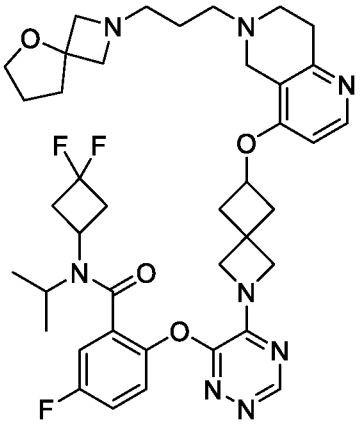


This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalents of 1-bromo-3-chloropropane, except that 1 equivalent of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was used to obtain crude 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-

difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide. This material was used without further purification.

Yield: 50%; LCMS (Method G): Rt = 2.02 min, m/z = 686.1 $[M+H]^+$, 53.48%.

Step 4. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

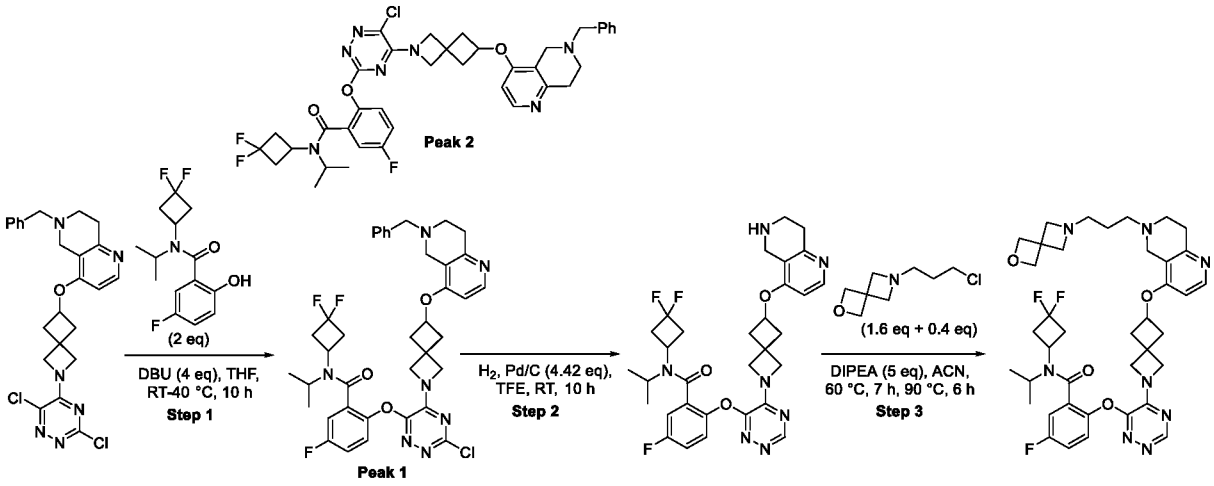


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride was used. The reaction was stirred at 90 °C. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by Prep HPLC (Method V). The product fractions were concentrated under reduced pressure and lyophilized to afford 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

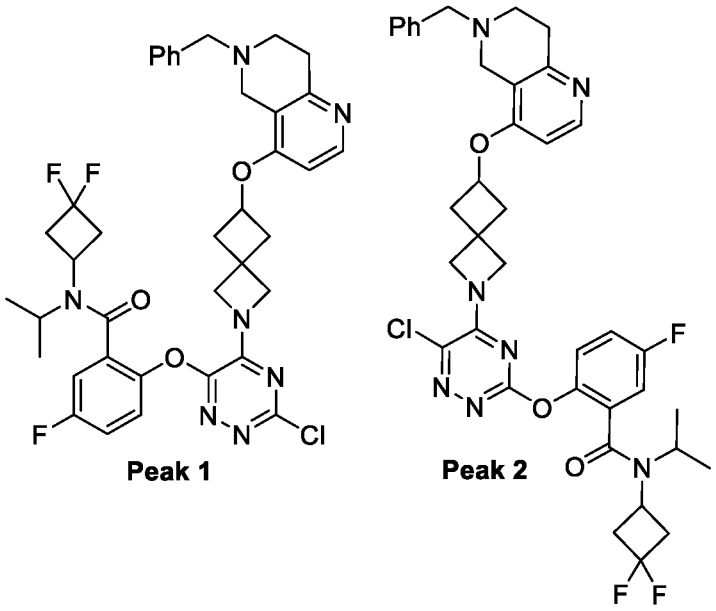
Yield: 4.65%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.34 (m, 3H), 6.67 (br s, 1H), 4.79 (quin, J = 6.7 Hz, 1H), 4.69 - 4.50 (m, 2H), 4.29 - 4.11 (m, 2H), 3.92 - 3.79 (m, 1H), 3.65 (br t, J = 6.6 Hz, 4H), 3.40 (br s, 2H), 3.25-3.24 (m, 2H), 2.91 - 2.76 (m, 7H), 2.68 - 2.62 (m, 3H), 2.40 (br s, 2H), 2.01 - 1.94 (m, 3H), 1.80 (quin, J = 6.8 Hz, 3H), 1.50 (br s, 2H), 1.18 - 0.65 (m, 6H), three protons merged with solvent peaks;

LCMS (Method G): Rt = 1.87 min, m/z = 763.2 $[M+H]^+$; HPLC (Method A): Rt = 5.40 min, 96.99%.

Example 320. 2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 351)



Step 1. *2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide*

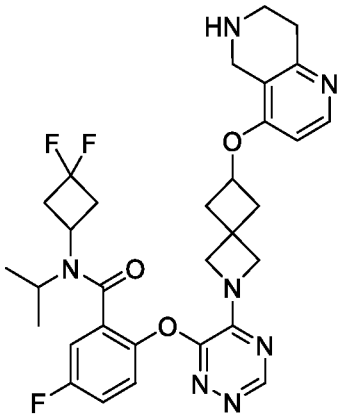


This compound was synthesized following the procedure described for the synthesis of Example 319, step 1. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5-10% MeOH in DCM), then by chiral Prep SFC (Method AA) to obtain peak 1, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide.

Yield: 36.9%; LCMS (Method G): Rt = 2.39 min, m/z = 734.2 $[M+H]^+$; HPLC (Method G): Rt = 7.32 min, 98.92%.

Note: Peak 2 was not isolated.

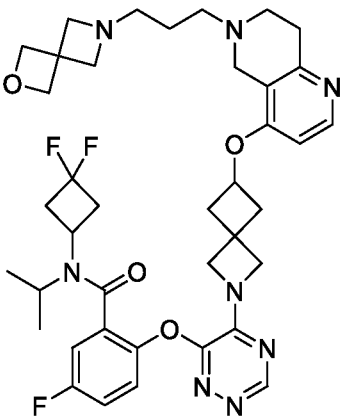
Step 2. N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 319, step 2, starting with 1 equivalent of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 4.42 equivalents of Pd-C was used. After completion, the filtrate was concentrated under reduced pressure to obtain crude *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid. This material was used without further purification.

Yield: 76%; LCMS (Method G): Rt = 1.73 min, m/z = 610.2 $[M+H]^+$, 87.31%.

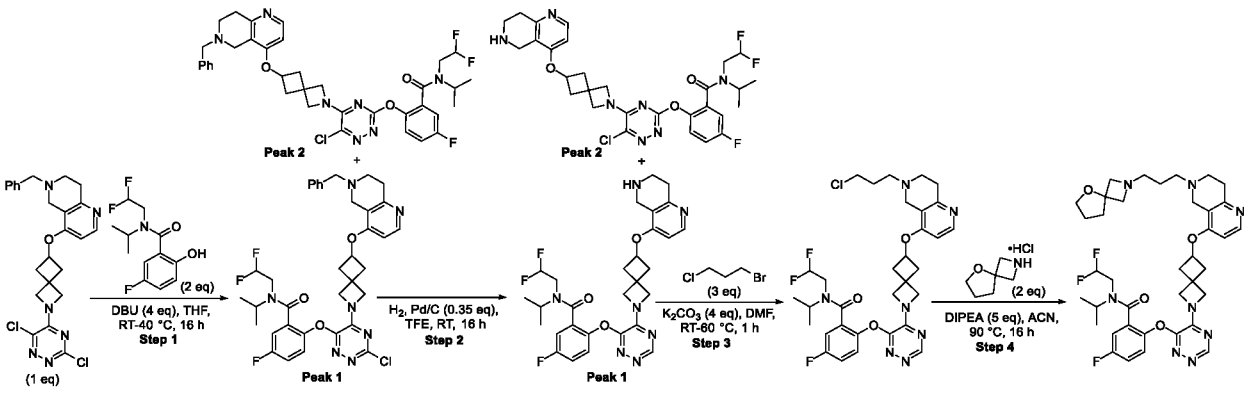
Step 3. 2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide



To a stirred solution of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-

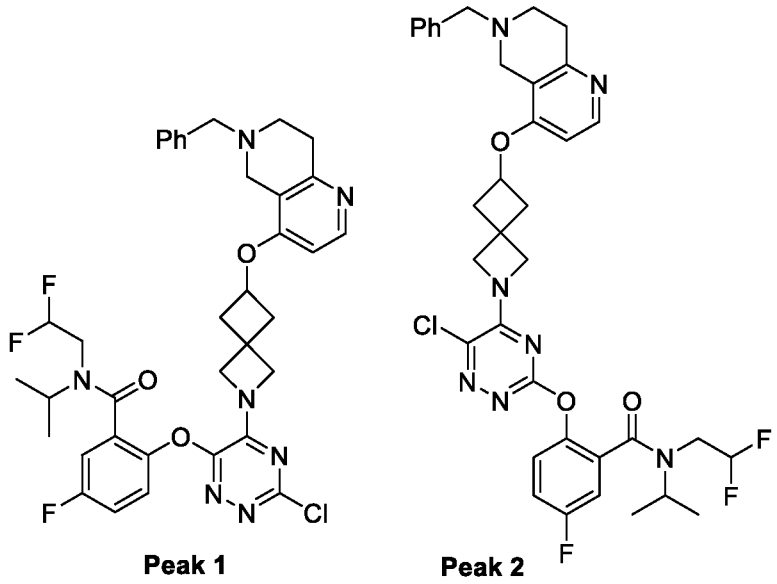
yl)oxy)benzamide (0.5 g, 0.820 mmol) in ACN (5 mL), DIPEA (0.740 mL, 4.10 mmol) and 6-(3-chloropropyl)-2-oxa-6-azaspiro[3.3]heptane (0.230 g, 1.312 mmol) were added at RT. The reaction was stirred at 60 °C for 7 h. The starting material was not consumed completely. Therefore, another lot of 6-(3-chloropropyl)-2-oxa-6-azaspiro[3.3]heptane (58 mg, 0.328 mmol) was added, and the reaction was stirred at 90 °C for 6 h. The reaction progress was monitored by LCMS and TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The isolated product was impure. Therefore, the compound was re-purified by Prep HPLC (Method AO) to afford 2-((5-(6-((6-(3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (64.4 mg, 9.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.34 (m, 3H), 6.67 (br s, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.70 - 4.51 (m, 6H), 4.32 - 4.13 (m, 2H), 3.94 - 3.79 (m, 1H), 3.77 - 3.51 (m, 2H), 3.39 (br s, 2H), 3.21 (br s, 4H), 2.87 - 2.75 (m, 4H), 2.73 - 2.56 (m, 5H), 2.47 - 2.40 (m, 2H), 2.39 - 2.23 (m, 4H), 1.46 (br s, 2H), 1.19 – 0.61 (m, 6H); LCMS (Method L): Rt = 1.61 min, m/z = 749.5 $[M+H]^+$; HPLC (Method G): Rt = 5.04 min, 99.60%.

Example 321. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 352)



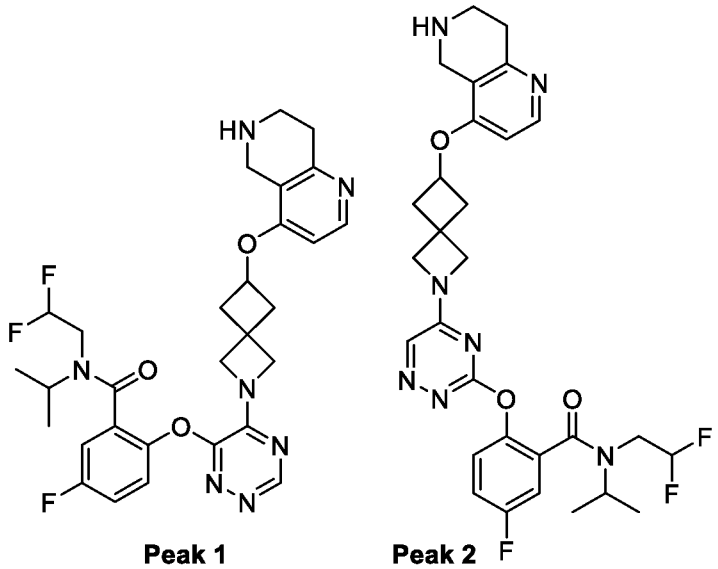
Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-

isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



These compounds were synthesized following the procedure described for the synthesis of Example 54, Step 4, starting with 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine, except that 2 equivalents of *N*-(2,2-difluoroethyl)-5-fluoro-2-hydroxy-*N*-isopropylbenzamide was used. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (products were eluted at 95-100% EtOAc in hexane) to obtain a mixture of both regioisomers, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide and the other regioisomer (3.15 g, 31.9% yield) as semi-solids. LCMS (Method G): Rt = 2.38 min, m/z = 708.5 $[M+H]^+$, 82.29%. The mixture of regioisomers were used without further purification.

Step 2. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide



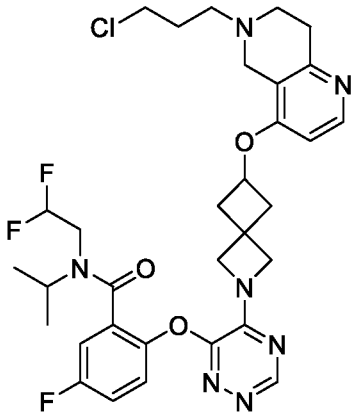
These compounds were synthesized following the procedure described for the synthesis of Example 54, step 5, starting with 1 equivalent of a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide and the other regioisomer. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford a mixture of regioisomers. The regioisomers were separated by achiral Prep SFC (Method O) to obtain both regioisomers as solids.

Peak 1. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (480 mg, 22.05% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 - 8.44 (m, 1H), 8.18 (d, J = 5.7 Hz, 1H), 7.51 - 7.45 (m, 1H), 7.44 - 7.37 (m, 2H), 6.67 (d, J = 5.7 Hz, 1H), 6.37 - 5.98 (m, 1H), 4.81 - 4.72 (m, 1H), 4.66 - 4.42 (m, 2H), 4.29 - 4.10 (m, 2H), 3.77 - 3.73 (m, 1H), 3.71 (br s, 2H), 3.65 - 3.46 (m, 1H), 2.96 (t, J = 5.6 Hz, 2H), 2.86 - 2.78 (m, 2H), 2.69 (t, J = 5.5 Hz, 2H), 2.38 - 2.25 (m, 2H), 2.08 (br s, 2H), 1.17 - 1.00 (m, 3H), 0.80 - 0.65 (m, 3H); LCMS (Method G): Rt = 1.50 min, m/z = 584.1 $[M+H]^+$, 93.14%.

Peak 2. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)benzamide (440 mg, 20.27% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 - 8.34 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.39 - 7.29 (m, 3H), 6.66 (d, J = 5.6 Hz, 1H), 6.18 - 5.85 (m, 1H), 4.82 - 4.71 (m,

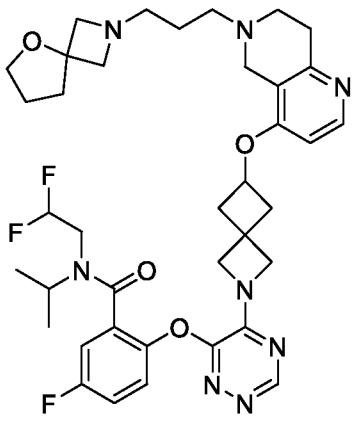
1H), 4.37 - 4.24 (m, 2H), 4.16 - 4.02 (m, 2H), 3.86 - 3.77 (m, 1H), 3.71 (br s, 2H), 3.66 - 3.52 (m, 1H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.87 - 2.77 (m, 2H), 2.69 (br t, *J* = 5.6 Hz, 2H), 2.36 - 2.26 (m, 2H), 2.08 (br s, 2H), 1.14 - 1.00 (m, 3H), 0.95 - 0.85 (m, 3H); LCMS (Method G): Rt = 1.55 min, m/z = 584.1 $[M+H]^+$, 93.40%.

Step 3. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



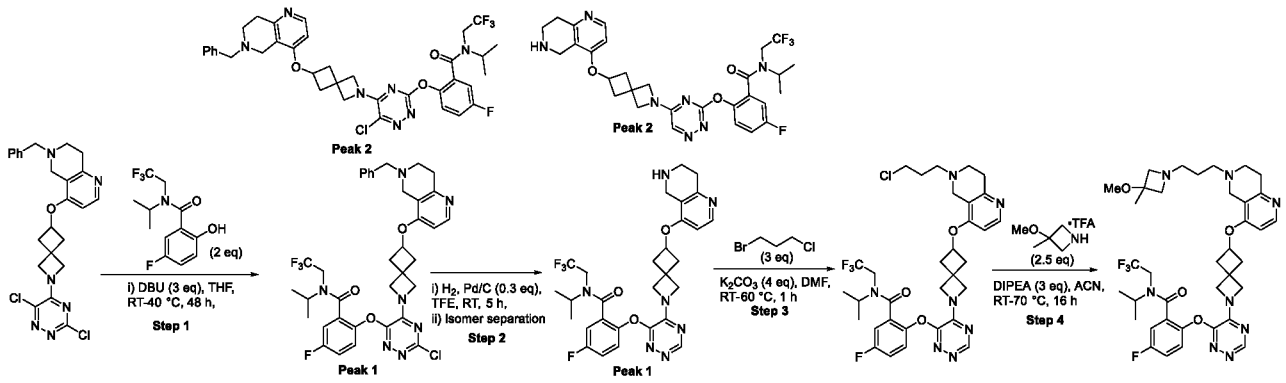
This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 1-bromo-3-chloropropane , except that 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was used, to obtain crude 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (0.420 g, 62.7% yield) as a semi-solid. LCMS (Method G): Rt = 2.25 min, m/z = 660.3 $[M+H]^+$, 81.10%. This material was used without further purification.

Step 4. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide

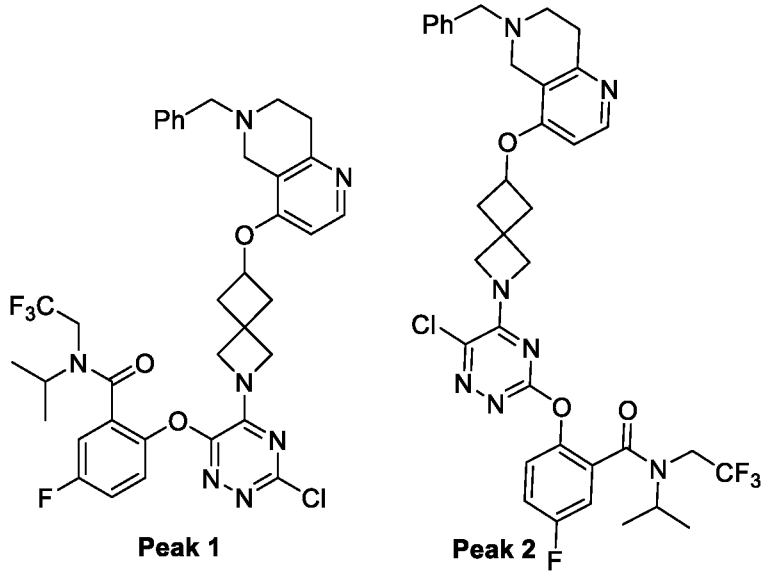


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride. The reaction was stirred at 90 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (125.53 mg, 25.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.37 (m, 2H), 6.69 (d, J = 5.7 Hz, 1H), 6.37 - 5.98 (m, 1H), 4.84 - 4.73 (m, 1H), 4.66 - 4.39 (m, 2H), 4.29 - 4.09 (m, 2H), 3.78 - 3.68 (m, 2H), 3.65 (t, J = 6.7 Hz, 2H), 3.61-3.49 (m, 1H), 3.40 (br s, 2H), 3.27 - 3.22 (m, 2H), 2.90 - 2.86 (m, 2H), 2.86 - 2.77 (m, 4H), 2.69 - 2.63 (m, 2H), 2.48 -2.37 (m, 4H), 2.01 - 1.95 (m, 2H), 1.85 - 1.75 (m, 2H), 1.50 (br s, 2H), 1.07 (br s, 3H), 0.73 (br s, 3H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.68 min, m/z = 737.2 $[M+H]^+$; HPLC (Method A): Rt = 5.07 min, 96.21%.

Example 322. 5-Fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 318)



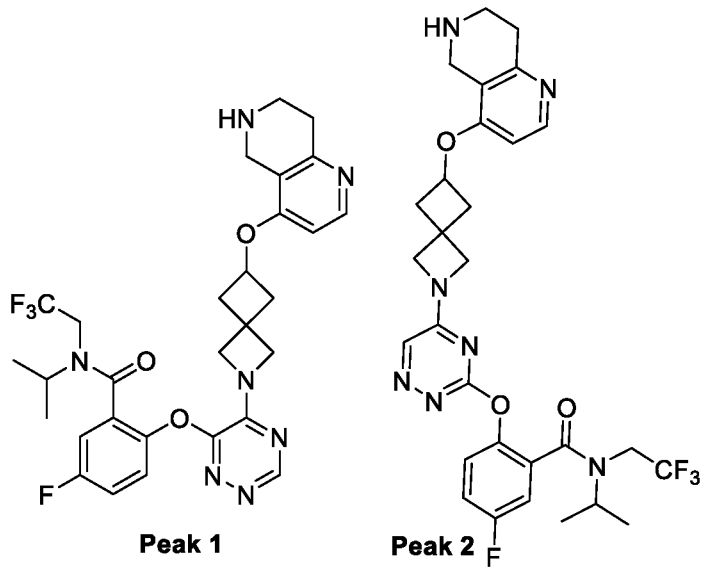
Step 1. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide and 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



These compounds were synthesized following the procedure described for the synthesis of Intermediate 56, Step 1, to obtain 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide.

Yield: 67.9%. LCMS (Method G): Rt = 2.35 min, m/z = 726.5 $[M+H]^+$, 95.52%.

Step 2. 5-Fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide and 5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



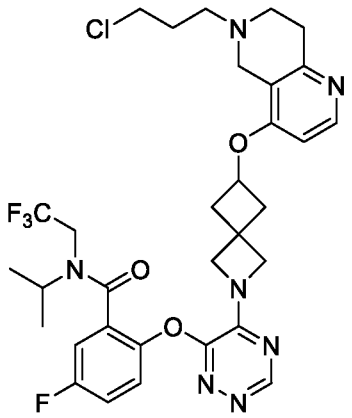
The reaction was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Example 319, step 2, starting with 1 equivalent of a mixture of 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide, except that 0.3 equivalent of Pd/C was used. After completion, the reaction mixtures from both batches were filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol. The combined filtrate was concentrated under reduced pressure to afford the crude mixture of regioisomers. This mixture was purified by achiral Prep SFC (Method N). Product fractions were concentrated under reduced pressure to obtain both regioisomers. An impurity was observed in the purified compound (peak 1). Therefore, peak 1 was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Combined yield: 26.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.53 - 7.38 (m, 3H), 6.72 - 6.58 (m, 1H), 4.76 (quin, J = 6.6 Hz, 1H), 4.67 - 4.40 (m, 2H), 4.37 - 3.93 (m, 4H), 3.86 - 3.74 (m, 1H), 3.70 (s, 2H), 2.95 (br t, J = 5.6 Hz, 2H), 2.89 - 2.73 (m, 2H), 2.72 - 2.64 (m, 2H), 2.34 - 2.20 (m, 2H), 1.27 - 0.66 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.68 min, m/z = 602.5 $[M+H]^+$; HPLC (Method A): Rt = 4.55 min, 99.53%.

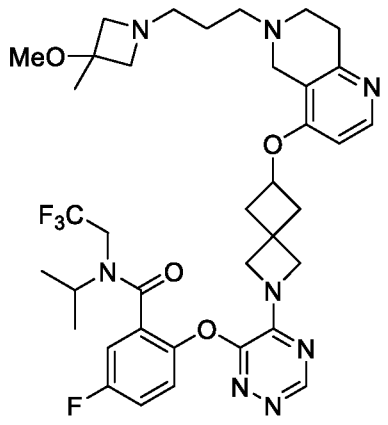
Step 3. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 56, Step 3. After work up, the crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to obtain 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 20.65%; LCMS (Method G): Rt = 2.02 min, m/z = 678.5 $[M+H]^+$, 98.32%.

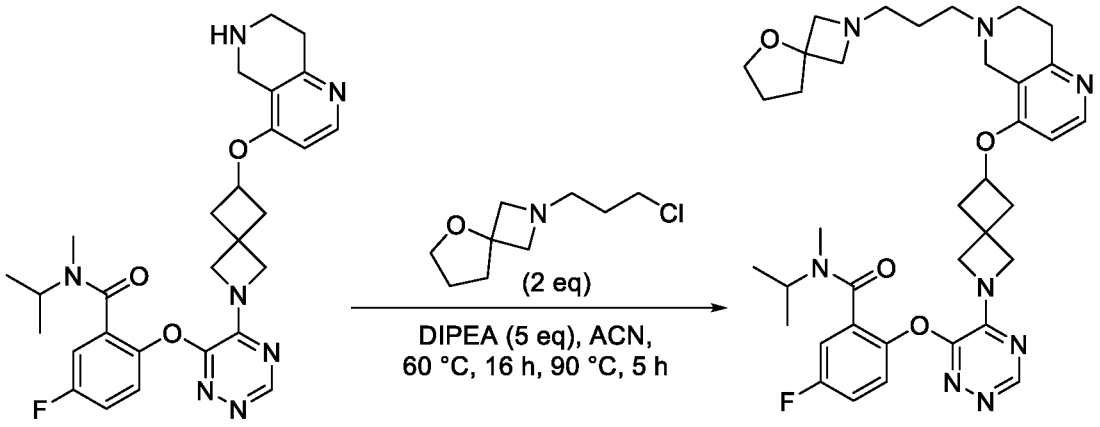
Step 4. 5-Fluoro-N-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 2.5 equivalents of 3-methoxy-3-methylazetidine 2,2,2-trifluoroacetate, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 47.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.51 - 7.40 (m, 3H), 6.73 - 6.63 (m, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.66 - 4.44 (m, 2H), 4.32 - 3.99 (m, 4H), 3.84 - 3.72 (m, 1H), 3.40 (s, 2H), 3.12 - 3.05 (m, 5H), 2.87 - 2.77 (m, 6H), 2.69 - 2.63 (m, 2H), 2.44 - 2.24 (m, 5H), 1.51 (br s, 2H), 1.36 (s, 3H), 1.26 - 0.67 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.78 min, m/z = 743.4 $[M+H]^+$; HPLC (Method A): Rt = 5.11 min, 98.02%.

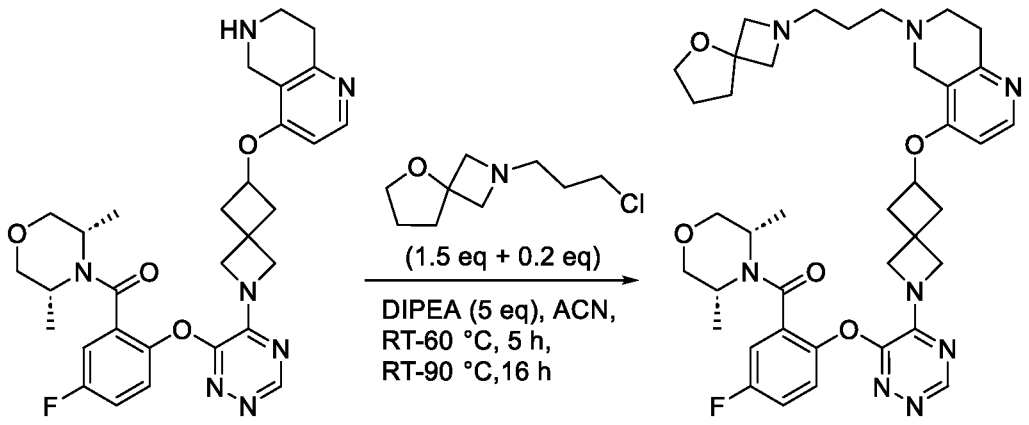
Example 323. 2-((5-(6-((6-(3-(5-Oxa-2-Azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide (Compound No. 353)



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent 5-fluoro-*N*-isopropyl-*N*-methyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 2 equivalents of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C for 16 h and then at 90 °C for 5 h. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide as a solid.

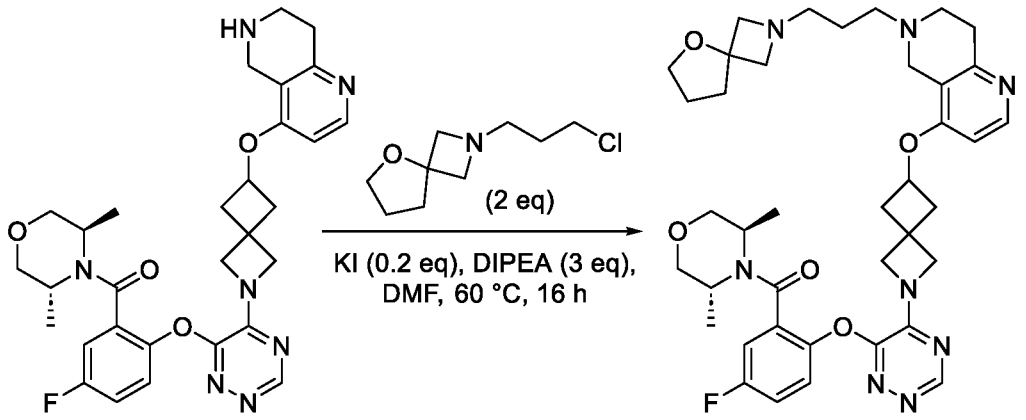
Yield: 6.22%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 5.7 Hz, 1H), 7.51 - 7.41 (m, 1H), 7.39 - 7.30 (m, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.83 - 4.76 (m, 1H), 4.65 - 4.45 (m, 2H), 4.27 - 4.13 (m, 2H), 3.68-3.66 (m, 1H), 3.65 (t, J = 6.7 Hz, 2H), 3.40 (br s, 2H), 3.27 - 3.22 (m, 2H), 2.91 - 2.75 (m, 8H), 2.70 - 2.63 (m, 2H), 2.57 (s, 3H), 2.42 - 2.35 (m, 4H), 2.00 - 1.94 (m, 2H), 1.84 - 1.75 (m, 2H), 1.56 - 1.44 (m, 2H), 1.14 - 0.73 (m, 6H); LCMS (Method G): Rt = 1.68 min, m/z = 687.3 $[M+H]^+$; HPLC (Method G): Rt = 4.59 min, 99.73%.

Example 324. (2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*S*,5*R*)-3,5-dimethylmorpholino)methanone (Compound No. 354)



To a stirred solution of ((3*R*,5*S*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone (0.3 g, 0.521 mmol) in ACN (3 mL), 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (0.148 g, 0.782 mmol) and *N*,*N*-diisopropylethylamine (0.454 mL, 2.61 mmol) were added at RT. The reaction was stirred at 60 °C for 5 h. The starting material was not consumed. Therefore, another lot of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane (0.020 g, 0.104 mmol) was added at RT, and the reaction was stirred at 90 °C for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure, water (50 mL) was added, and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*S*)-3,5-dimethylmorpholino)methanone (0.07 g, 18.06% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 8.19 (d, *J* = 5.6 Hz, 1H), 7.53 - 7.34 (m, 3H), 6.68 (d, *J* = 5.6 Hz, 1H), 4.84 - 4.72 (m, 1H), 4.67 - 4.41 (m, 2H), 4.39 - 4.12 (m, 3H), 3.77 - 3.50 (m, 5H), 3.40 (s, 2H), 3.24 (br d, *J* = 6.0 Hz, 3H), 2.91 - 2.76 (m, 7H), 2.68 - 2.61 (m, 2H), 2.43 - 2.27 (m, 4H), 2.02 - 1.95 (m, 2H), 1.80 (quin, *J* = 6.8 Hz, 2H), 1.50 (br s, 2H), 1.35 - 1.10 (m, 6H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.73 min, m/z = 729.3 $[M+H]^+$; HPLC (Method G): Rt = 4.57 min, 99.11%.

Example 325. (2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone (Compound No. 355)

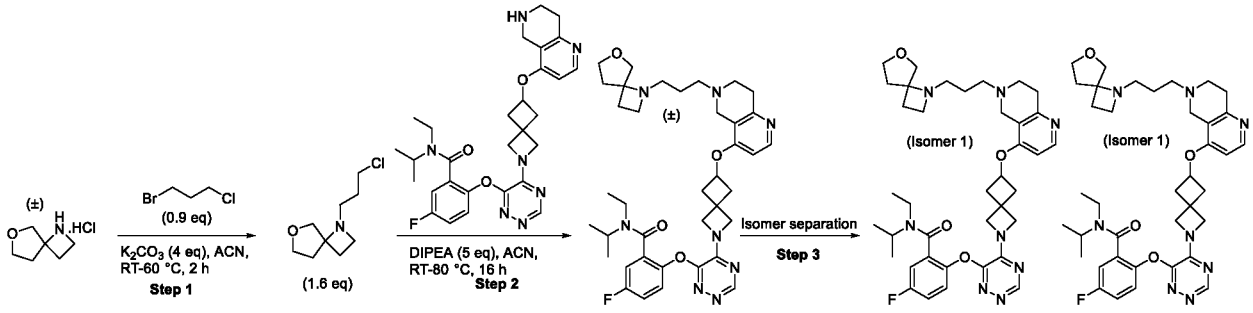


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 2 equivalents of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane and 1 equivalent of ((3*R*,5*R*)-3,5-dimethylmorpholino)(5-fluoro-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)phenyl)methanone, except that 0.2 equivalent of KI was used. The reaction was stirred at 60 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluorophenyl)((3*R*,5*R*)-3,5-dimethylmorpholino)methanone as a solid.

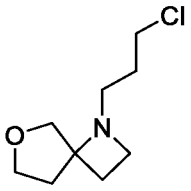
Yield: 20.60%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.49 - 7.35 (m, 3H), 6.68 (br d, J = 5.5 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.73 - 4.43 (m, 2H), 4.35 - 4.13 (m, 2H), 3.95 - 3.52 (m, 6H), 3.40 (br s, 3H), 3.25 (br dd, J = 2.0, 5.7 Hz, 3H), 2.93 - 2.74 (m, 7H), 2.72 - 2.62 (m, 2H), 2.45 - 2.30 (m, 5H), 2.02 - 1.94 (m, 2H), 1.80 (quin, J = 6.9 Hz, 2H), 1.60 - 1.38 (m, 2H), 1.13 (br d, J = 4.9 Hz, 6H); LCMS (Method G): Rt = 1.53 min, m/z = 729.2 $[M+H]^+$; HPLC (Method G): Rt = 4.52 min, 97.85%; Chiral SFC (Method V): Rt = 3.05 min, 100%.

Example 326. (*E1*)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 356)

Example 327. (*E2*)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 357)



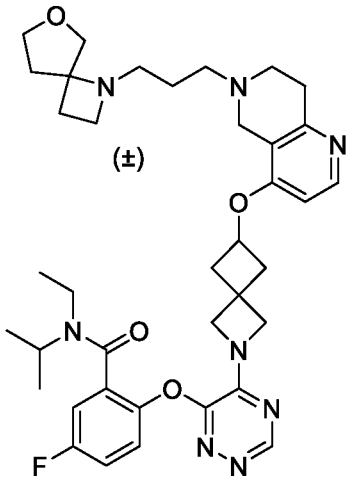
Step 1. (±)-1-(3-Chloropropyl)-6-oxa-1-azaspiro[3.4]octane



This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.9 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent 6-oxa-1-azaspiro[3.4]octane hydrochloride was used. After work-up, the filtrate was concentrated under reduced pressure to afford crude (±)-1-(3-chloropropyl)-6-oxa-1-azaspiro[3.4]octane. This material was used without further purification.

Yield: 67.0%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 - 3.86 (m, 2H), 3.82 - 3.71 (m, 1H), 3.65 - 3.57 (m, 3H), 3.24 - 3.06 (m, 2H), 2.63 (br t, *J* = 7.0 Hz, 2H), 2.35 - 2.10 (m, 3H), 2.01 - 1.90 (m, 1H), 1.84 (quin, *J* = 6.7 Hz, 2H); LCMS-ELSD (Method G): Rt = 0.39 min, m/z = 190.1 $[M+H]^+$, 70.74%.

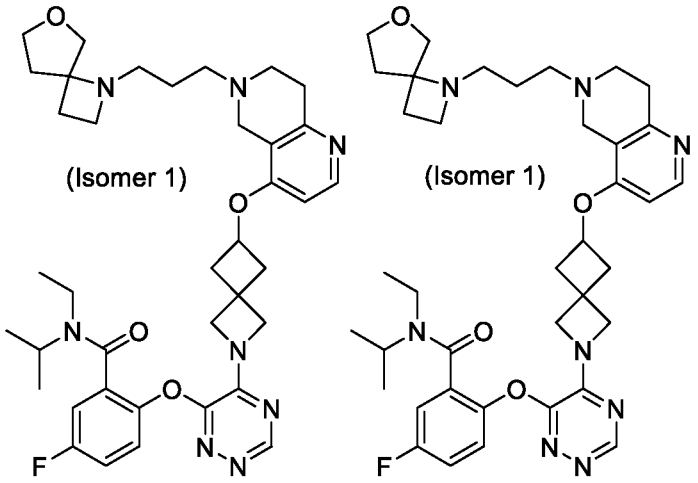
Step 2. (±)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 1.6 equivalents of (±)-1-(3-chloropropyl)-6-oxa-1-azaspiro[3.4]octane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 80 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (±)-2-((5-(6-((6-(3-(6-oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 45.8%; LCMS (Method G): Rt = 1.69 min, m/z = 701.4 $[M+H]^+$; HPLC (Method G): Rt = 4.69 min, 94.95%.

Step 3. (E1)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((5-(6-((6-(3-(6-oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

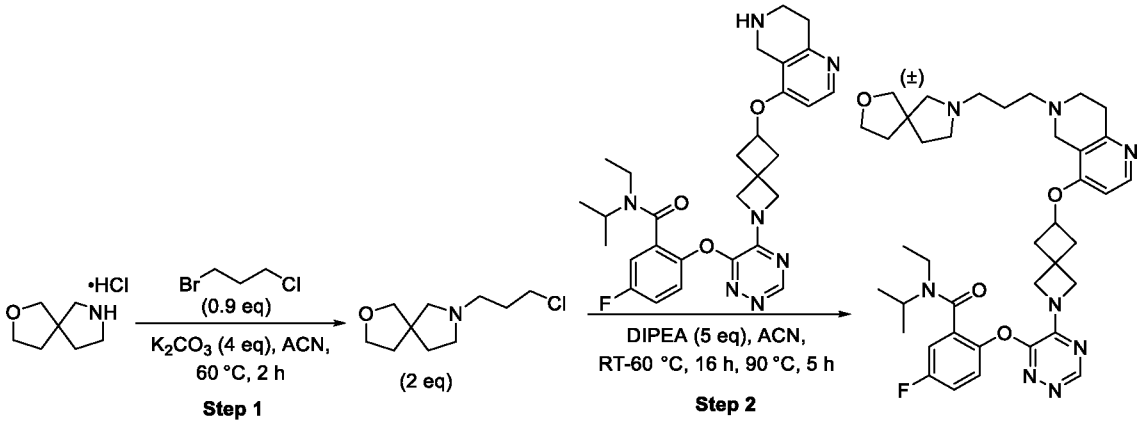


(±)-2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.185 g, 0.264 mmol) was purified by chiral Prep HPLC (Method B). The product fractions were concentrated under reduced pressure to obtain both enantiomers. An impurity was observed in the ^{1}HNMR spectrum of the isolated compounds. Therefore, both isomers were re-purified individually by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*E1*)-2-((5-(6-((6-(3-(6-oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (34.48 mg, 18.32% yield) and (*E2*)-2-((5-(6-((6-(3-(6-oxa-1-azaspiro[3.4]octan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (27.74 mg, 14.58% yield) as solids.

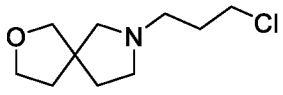
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.31 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.67 - 4.49 (m, 2H), 4.32 - 4.11 (m, 2H), 3.77 - 3.57 (m, 4H), 3.50 - 3.37 (m, 4H), 3.17 - 2.90 (m, 4H), 2.85 - 2.76 (m, 4H), 2.70 - 2.64 (m, 1H), 2.43 - 2.26 (m, 4H), 2.19 - 1.96 (m, 3H), 1.94 - 1.80 (m, 1H), 1.60 - 1.47 (m, 2H), 1.15 - 0.64 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.70 min, m/z = 701.4 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 98.29%; Chiral HPLC (Method AAO): Rt = 5.57 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.68 - 4.49 (m, 2H), 4.32 - 4.12 (m, 2H), 3.78 - 3.58 (m, 4H), 3.47 - 3.39 (m, 4H), 3.16 - 2.89 (m, 4H), 2.86 - 2.77 (m, 4H), 2.69 - 2.63 (m, 1H), 2.43 - 2.26 (m, 4H), 2.19 - 1.96 (m, 3H), 1.89 - 1.79 (m, 1H), 1.49 (br s, 2H), 1.18 - 0.67 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.71 min, m/z = 701.4 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 97.25%; Chiral SFC (Method AAO): Rt = 6.51 min, 96.02%.

Example 328. 2-((5-(6-((6-(3-(2-Oxa-7-Azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 358)



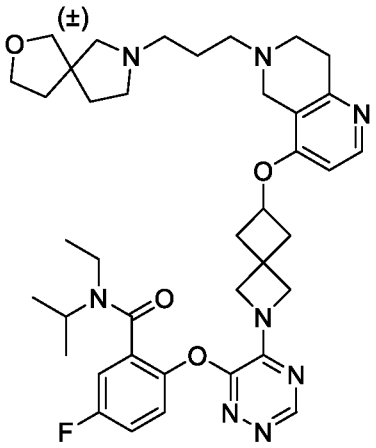
Step 1. (±)-7-(3-Chloropropyl)-2-oxa-7-azaspiro[4.4]nonane



This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.9 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of 2-oxa-7-azaspiro[4.4]nonane hydrochloride was used. After work-up, the filtrate was concentrated under reduced pressure to afford crude (±)-7-(3-chloropropyl)-2-oxa-7-azaspiro[4.4]nonane (0.270 g, 55% yield) as a solid. This material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 - 3.81 (m, 2H), 3.70 (d, J = 8.1 Hz, 1H), 3.62 (t, J = 6.6 Hz, 1H), 3.57 (d, J = 8.1 Hz, 1H), 2.71 - 2.47 (m, 5H), 2.44 (d, J = 9.1

Hz, 1H), 2.03 - 1.88 (m, 5H), 1.88 - 1.79 (m, 2H); LCMS ELSD (Method G): Rt = 1.30 min, m/z = 204.1 $[M+H]^+$, 75.49%.

Step 2. (±)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



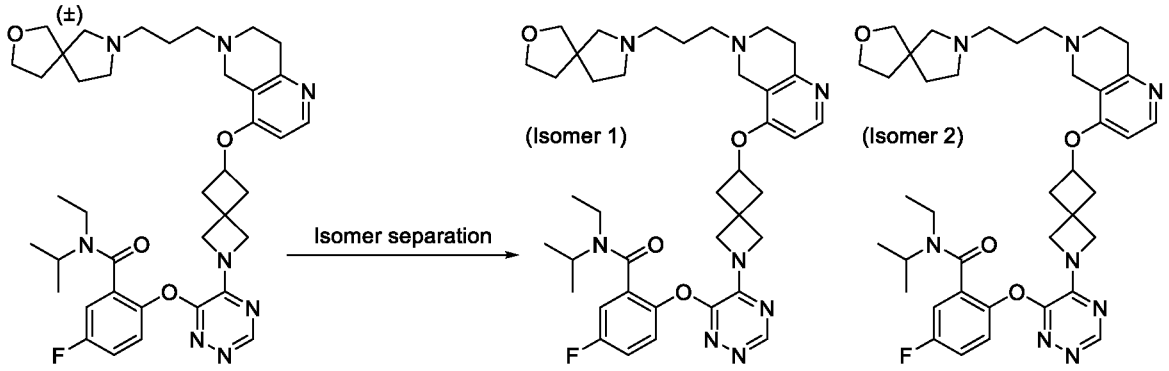
This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 2 equivalents of (±)-7-(3-chloropropyl)-2-oxa-7-azaspiro[4.4]nonane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C for 16 h and 90 °C for 5 h. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((5-(6-((6-(3-(2-oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 39.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.84 - 4.74 (m, 1H), 4.67 - 4.48 (m, 2H), 4.34 - 4.07 (m, 2H), 3.71 (t, J = 6.2 Hz, 2H), 3.68 - 3.58 (m, 2H), 3.57-3.49 (m, 1H), 3.42 (br s, 4H), 3.16 - 2.96 (m, 2H), 2.88 - 2.76 (m, 4H), 2.61 - 2.55 (m, 2H), 2.44-2.35 (m, 4H), 1.92 - 1.76 (m, 3H), 1.73 (t, J = 6.8 Hz, 2H), 1.66 (br s, 3H), 1.16 - 0.92 (m, 7H), 0.76 - 0.67 (m, 2H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.58 min, m/z

= 715.3 $[M+H]^+$; HPLC (Method G): Rt = 4.74 min, 95.48%; Chiral HPLC (Method A): Peak 1: Rt = 18.64 min, 49.85%; Peak 2: Rt = 21.82 min, 50.15%.

Example 329. (*E1*)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 359)

Example 330. (*E2*)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 360)



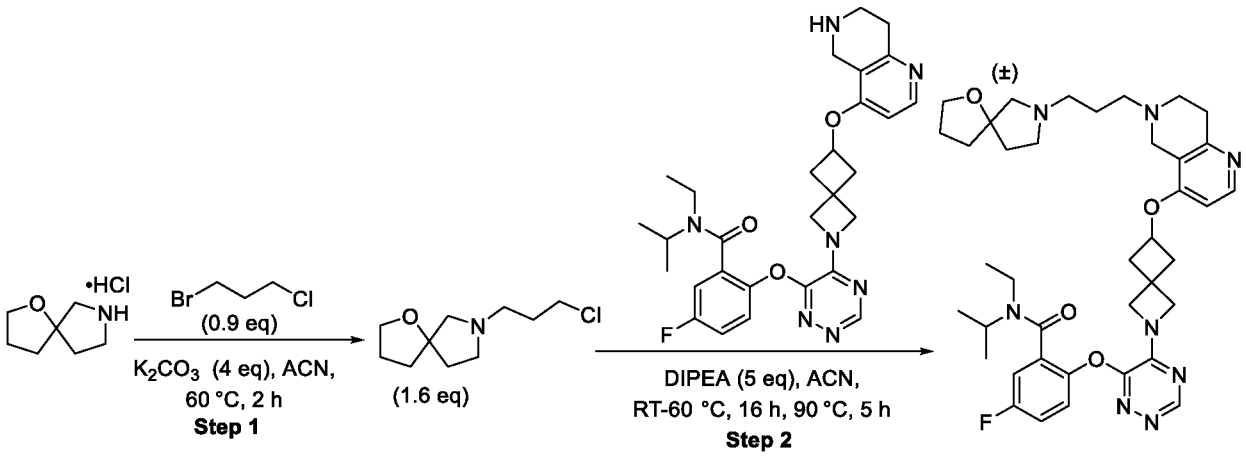
(±)-2-((5-(6-((6-(3-(2-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (150 mg, 0.210 mmol) was purified by chiral Prep HPLC (Method A) to obtain (*E1*)-2-((5-(6-((6-(3-(2-oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (5.34 mg, 3.44% yield) and (*E2*)-2-((5-(6-((6-(3-(2-oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (11.6 mg, 7.67% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.69 (d, J = 5.6 Hz, 1H), 4.83 - 4.75 (m, 1H), 4.66 - 4.49 (m, 2H), 4.33 - 4.10 (m, 2H), 3.77-3.68 (m, 2H), 3.66 - 3.57 (m, 1H), 3.56 - 3.49 (m, 2H), 3.44 - 3.40 (m, 4H), 3.14 - 2.99 (m, 2H), 2.88 - 2.77 (m, 4H), 2.43 - 2.35 (m, 6H), 1.92 - 1.78

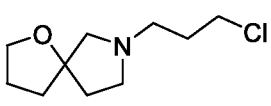
(m, 3H), 1.73 (t, *J* = 6.9 Hz, 2H), 1.65 (br s, 3H), 1.16 - 0.92 (m, 7H), 0.77 - 0.66 (m, 2H), two protons merged with solvent peak; LCMS (Method B): Rt = 1.05 min, m/z = 715.2 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 95.45%; Chiral HPLC (Method A): Rt = 18.72 min, 99.73%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.68 (d, *J* = 5.6 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.67 - 4.49 (m, 2H), 4.33 - 4.11 (m, 2H), 3.78 - 3.67 (m, 2H), 3.65 - 3.57 (m, 1H), 3.56 - 3.51 (m, 2H), 3.45 - 3.39 (m, 4H), 3.15 - 2.99 (m, 2H), 2.89 - 2.76 (m, 4H), 2.44 - 2.34 (m, 6H), 1.91 - 1.77 (m, 3H), 1.73 (t, *J* = 6.9 Hz, 2H), 1.64 (br s, 3H), 1.16 - 0.93 (m, 7H), 0.76 - 0.67 (m, 2H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.61 min, m/z = 715.3 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 97.88%; Chiral HPLC (Method A): Rt = 22.21 min, 98.67%.

Example 331. (±)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 361)

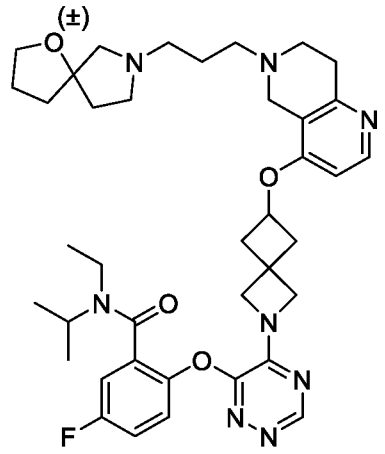


Step 1. (±)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane



This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.9 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of (±)-1-oxa-7-azaspiro[4.4]nonane hydrochloride was used. After work-up, the filtrate was concentrated under reduced pressure to afford crude (±)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane. This material was used without further purification.
Yield: 24%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 - 3.79 (m, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.80 - 2.67 (m, 2H), 2.64 - 2.55 (m, 4H), 2.06 - 1.83 (m, 8H).

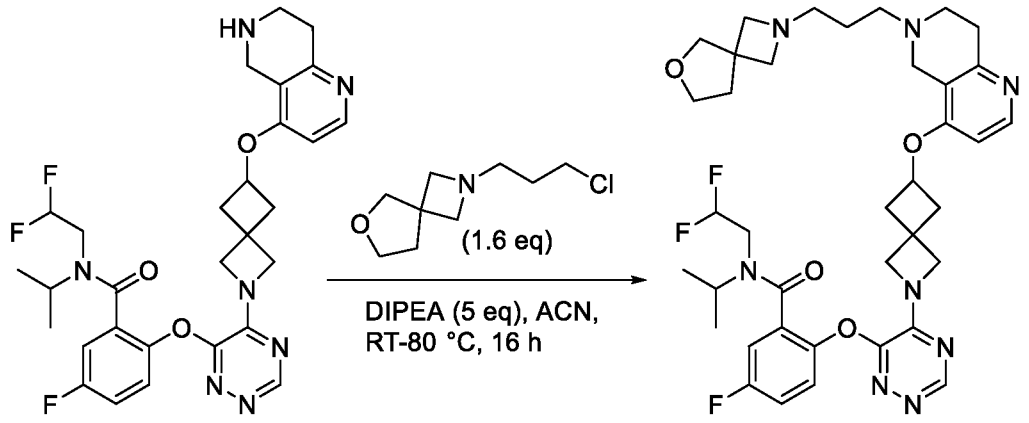
Step 2. (±)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 1.6 equivalents of (±)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C for 16 h and 90 °C for 5 h. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((5-(6-((6-(3-(1-oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.
Yield: 33.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.69 (d, *J* = 5.8 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.67 - 4.49

(m, 2H), 4.34 - 4.11 (m, 2H), 3.72 - 3.58 (m, 3H), 3.42 (br s, 2H), 3.16 - 2.98 (m, 2H), 2.88 - 2.77 (m, 4H), 2.71 - 2.66 (m, 2H), 2.48 - 2.43 (m, 4H), 2.42 - 2.35 (m, 4H), 1.86 - 1.73 (m, 6H), 1.69 - 1.60 (m, 2H), 1.16 - 0.93 (m, 7H), 0.75 - 0.68 (m, 2H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.70 min, m/z = 715.3 $[M+H]^+$; HPLC (Method G): Rt = 4.89 min, 96.74%; Chiral SFC (Method AAC): Peak 1: Rt = 7.80 min, 51.42%; Peak 2: Rt = 8.06 min, 48.57%.

Example 332. 2-((5-(6-((6-(3-(6-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 362)

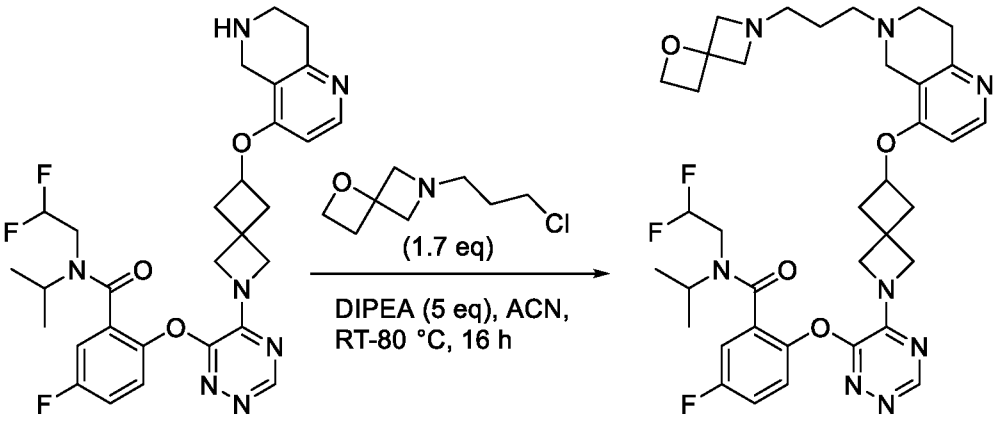


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 1.6 equivalents of 2-(3-chloropropyl)-6-oxa-2-azaspiro[3.4]octane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 80 °C. The reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 37.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.51 - 7.38 (m, 3H), 6.69 (d, J = 5.6 Hz, 1H), 6.37 - 5.97 (m, 1H), 4.83 - 4.72 (m, 1H), 4.64 - 4.44

(m, 2H), 4.30 - 4.11 (m, 2H), 3.80 - 3.49 (m, 8H), 3.43 - 3.38 (m, 3H), 3.06 (br s, 4H), 2.89 - 2.77 (m, 4H), 2.70 - 2.63 (m, 2H), 2.47 - 2.29 (m, 5H), 1.97 (br t, J = 6.9 Hz, 2H), 1.49 (br s, 2H), 1.18 - 0.67 (m, 4H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.10 min, m/z = 737.5 $[M+H]^+$; HPLC (Method G): Rt = 4.83 min, 98.80%.

Example 333. 2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 363)

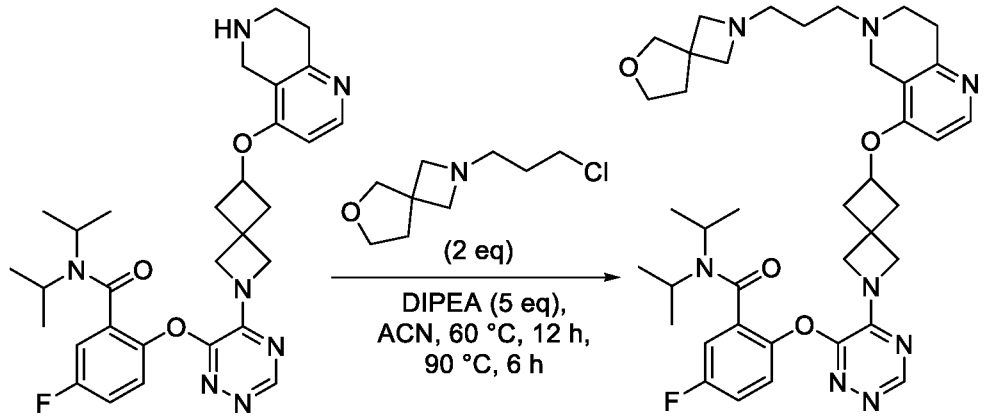


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 1.7 equivalents of 6-(3-chloropropyl)-1-oxa-6-azaspiro[3.3]heptane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 80 °C. The reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(1-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 12.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.53 - 7.36 (m, 3H), 6.69 (d, J = 5.6 Hz, 1H), 6.34 - 5.99 (m, 1H), 4.83 - 4.73 (m, 1H), 4.66 - 4.44 (m, 2H), 4.36 (br t, J = 7.5 Hz, 2H), 4.29 - 4.10 (m, 2H), 3.78 - 3.67 (m, 2H), 3.63 - 3.54 (m, 1H), 3.48 (br d, J = 6.4 Hz, 2H), 3.39 (br s, 2H), 2.95 (br d, J = 7.0 Hz, 2H), 2.86 - 2.76 (m,

4H), 2.73 (br t, *J* = 7.4 Hz, 2H), 2.69 - 2.62 (m, 2H), 2.47 - 2.29 (m, 6H), 1.48 (br s, 2H), 1.18 - 0.69 (m, 6H); LCMS (Method B): Rt = 1.06 min, m/z = 723.2 $[M+H]^+$; HPLC (Method G): Rt = 4.77 min, 99.07%.

Example 334. 2-((5-(6-((6-(3-(6-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (Compound No. 364)

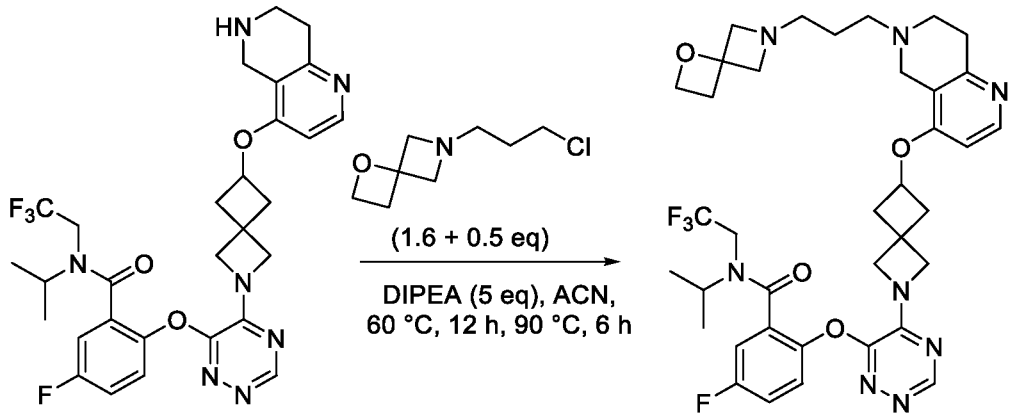


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 2 equivalents of 2-(3-chloropropyl)-6-oxa-2-azaspiro[3.4]octane and 1 equivalent of 5-fluoro-*N*,*N*-diisopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C for 12 h and 90 °C for 6 h. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide as a solid.

Yield: 19.21%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, *J* = 5.7 Hz, 1H), 7.44 (dd, *J* = 4.7, 8.9 Hz, 1H), 7.39 - 7.26 (m, 2H), 6.68 (d, *J* = 5.7 Hz, 1H), 4.79 (quin, *J* = 6.6 Hz, 1H), 4.72 - 4.50 (m, 2H), 4.36 - 4.08 (m, 2H), 3.67 (s, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.59 - 3.52 (m, 1H), 3.50 - 3.43 (m, 1H), 3.40 (s, 2H), 3.07 (br s, 4H), 2.89 - 2.74 (m, 4H), 2.71 - 2.61 (m, 3H), 2.43 - 2.25 (m, 5H), 1.97 (t, *J* = 6.8 Hz, 2H), 1.56 - 1.47 (m, 2H), 1.45 - 1.37 (m, 3H), 1.28 (br d, *J* = 6.1 Hz, 3H), 1.07 (br d, *J* = 6.4 Hz, 3H), 0.63 (br d, *J* = 6.3 Hz, 3H);

LCMS (Method G): Rt = 1.75 min, m/z = 715.3 $[M+H]^+$; HPLC (Method G): Rt = 4.88 min, 98.88%.

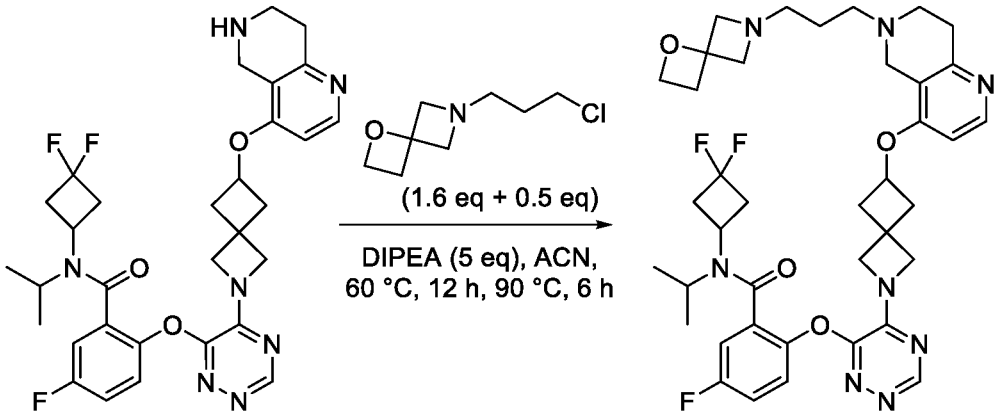
Example 335. 2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 365)



To a stirred solution of 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (600 mg, 0.997 mmol) in ACN (10 mL), DIPEA (0.871 mL, 4.99 mmol) and 6-(3-chloropropyl)-1-oxa-6-azaspiro[3.3]heptane (280 mg, 1.596 mmol) were added at RT. The reaction was stirred at 60 °C for 12 h. The reaction progress was monitored by LCMS and TLC (10% MeOH in DCM). Since the reaction was not complete, another lot of 6-(3-chloropropyl)-1-oxa-6-azaspiro[3.3]heptane (88 mg, 0.499 mmol) was added, and the reaction was continued at 90 °C for 6 h. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford 2-((5-(6-((6-(3-(1-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (117 mg, 15.68% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.7 Hz, 1H), 7.55 - 7.37 (m, 3H), 6.68 (br d, J = 3.9 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.68 - 4.43 (m, 2H), 4.36 (br t, J = 7.5 Hz, 2H), 4.31 - 3.99 (m, 4H), 3.86 - 3.71 (m, 1H), 3.48 (br d, J = 6.1 Hz, 2H), 3.39 (br s, 2H), 2.96 (br s, 2H), 2.88 - 2.61 (m, 9H), 2.42 - 2.25 (m, 5H), 1.59 - 1.38

(m, 2H), 1.23 - 0.65 (m, 6H); LCMS (Method G): Rt = 1.67 min, m/z = 741.4 $[M+H]^+$; HPLC (Method G): Rt = 4.93 min, 99.02%.

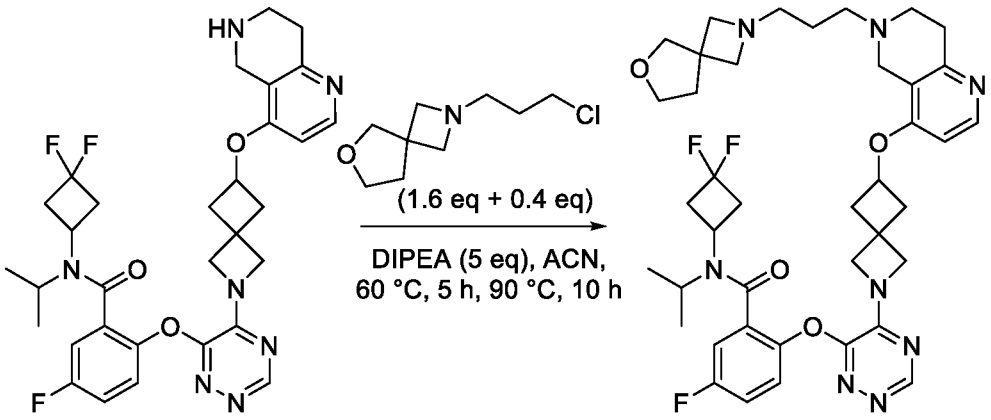
Example 336. 2-((5-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 366)



To a stirred solution of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (0.5 g, 0.820 mmol) in ACN (5 mL), DIPEA (0.740 mL, 4.10 mmol) and 6-(3-chloropropyl)-1-oxa-6-azaspiro[3.3]heptane (230 mg, 1.312 mmol) were added at RT. The reaction was stirred at 60 °C for 12 h. The starting material was not consumed completely. Therefore, another lot of 6-(3-chloropropyl)-1-oxa-6-azaspiro[3.3]heptane (72.0 mg, 0.410 mmol) was added, and the reaction was stirred at 90 °C for 6 h. The reaction progress was monitored by LCMS and TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The isolated product was impure. Therefore, the compound was re-purified by Prep HPLC (Method X) to afford 2-((5-(6-((6-(3-(1-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (69.22 mg, 11.12%; yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.51 - 7.35 (m, 3H), 6.67 (br s, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.71 - 4.47 (m, 2H), 4.36 (t, J = 7.4 Hz, 2H), 4.31 - 4.12 (m, 2H), 4.02 - 3.80 (m, 1H), 3.77 - 3.56 (m, 2H), 3.47 (br d, J = 7.1 Hz, 2H), 3.39 (br s, 2H), 2.94 (br d, J = 7.5 Hz,

2H), 2.89 - 2.61 (m, 11H), 2.47 - 2.40 (m, 2H), 2.39 - 2.29 (m, 4H), 1.48 (br s, 2H), 1.22 - 1.00 (m, 3H), 0.86 - 0.65 (m, 3H); LCMS (Method G): Rt = 1.81 min, m/z = 749.8 $[M+H]^+$; HPLC (Method G): Rt = 5.14 min, 99.75%.

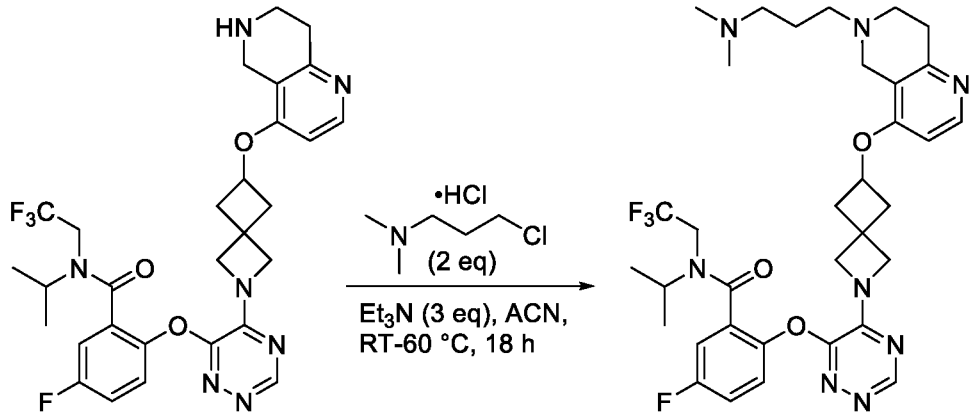
Example 337. 2-((5-(6-((6-(3-(6-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 367)



To a stirred solution of *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (0.5 g, 0.820 mmol) in ACN (5 mL), DIPEA (0.716 mL, 4.10 mmol) and 2-(3-chloropropyl)-6-oxa-2-azaspiro[3.4]octane (0.249 g, 1.312 mmol) were added at RT. The reaction was stirred at 60 °C for 5 h. The starting material was not consumed completely. Therefore, another lot of 2-(3-chloropropyl)-6-oxa-2-azaspiro[3.4]octane (0.062 g, 0.328 mmol) was added, and the reaction was stirred at 90 °C for 10 h. The reaction progress was monitored by LCMS and TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by Prep HPLC (Method AO) to obtain 2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (162 mg, 25.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.7 Hz, 1H), 7.53 - 7.33 (m, 3H), 6.67 (br s, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.68 - 4.47 (m, 2H), 4.33 - 4.10 (m, 2H), 3.91 - 3.77 (m, 1H), 3.67 (s, 2H), 3.66 - 3.57 (m, 3H), 3.40 (br s, 2H), 3.06 (br s, 4H), 2.89 - 2.77 (m, 4H), 2.74 - 2.62 (m, 4H), 2.48 - 2.43 (m, 2H), 2.42 - 2.25 (m, 4H), 1.97 (br t, J = 6.9 Hz, 2H), 1.58 - 1.35 (m, 2H), 1.22 - 0.57 (m, 6H), two protons merged with solvent peaks; LCMS

(Method G): Rt = 1.70 min, m/z = 763.3 $[M+H]^+$; HPLC (Method G): Rt = 5.07 min, 99.30%.

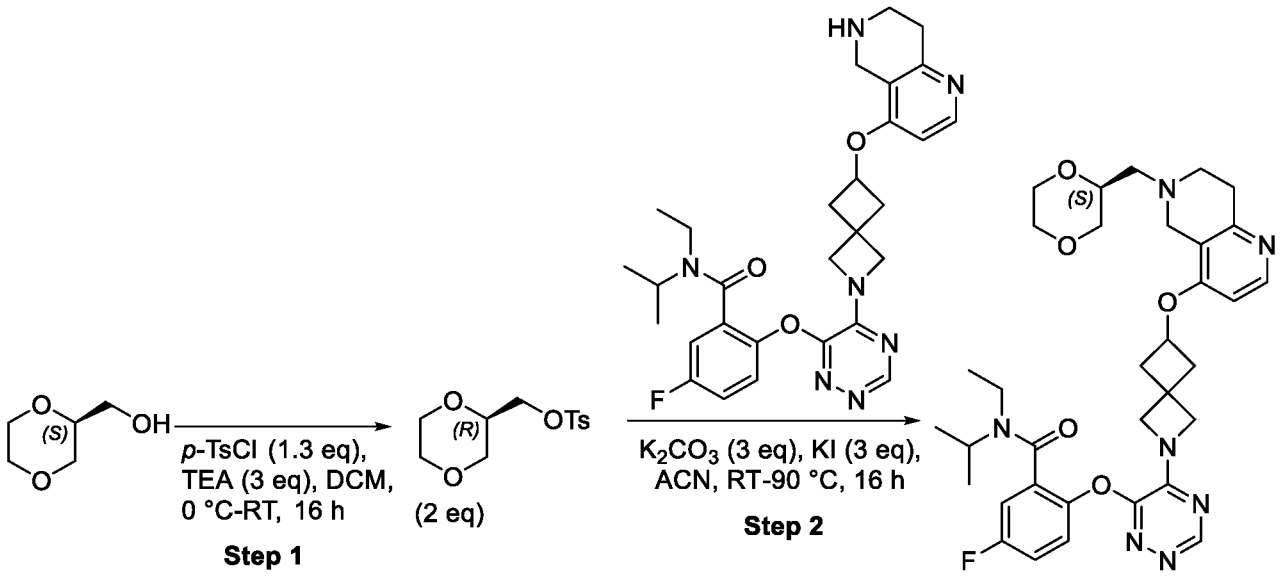
Example 338. 2-((5-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 319)



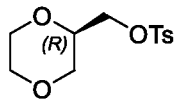
This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride, except that 1 equivalent of 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide and 3 equivalents of TEA were used. The reaction was stirred at 60 °C. The crude product was purified by Prep HPLC (Method V). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 19.24%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.52 - 7.39 (m, 3H), 6.69 - 6.68 (m, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.62 - 4.46 (m, 2H), 4.33 - 4.03 (m, 4H), 3.82 - 3.71 (m, 1H), 3.42 (s, 2H), 2.85 - 2.78 (m, 4H), 2.71 - 2.65 (m, 2H), 2.27 - 2.17 (m, 3H), 2.11 (s, 6H), 1.62 (br s, 2H), 1.14 - 0.69 (m, 6H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.81 min, m/z = 687.3 $[M+H]^+$; HPLC (Method A): Rt = 4.73 min, 99.82%.

Example 339. (*S*)-2-((5-(6-((6-((1,4-Dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 368)

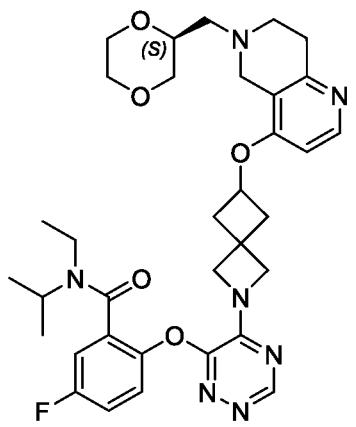


Step 1. (R)-(1,4-Dioxan-2-yl)methyl 4-methylbenzenesulfonate



In a 25 mL two neck round bottom flask under a nitrogen atmosphere, (*S*)-(1,4-dioxan-2-yl)methanol (500 mg, 4.23 mmol) was dissolved in DCM (10 mL). To this solution, TEA (1.180 mL, 8.47 mmol) and *p*-TsCl (1049 mg, 5.50 mmol) were added at 0 °C, and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with water (20 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 25% EtOAc in hexane) to obtain (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (700 mg, 60.1% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 - 7.76 (m, 2H), 7.50 (d, J = 8.0 Hz, 2H), 4.07 - 3.91 (m, 2H), 3.73 - 3.56 (m, 4H), 3.55 - 3.47 (m, 1H), 3.44 - 3.35 (m, 1H), 3.21 (dd, J = 9.8, 11.4 Hz, 1H), 2.43 (s, 3H); LCMS (Method G): Rt = 1.86 min, m/z = 290.1 $[M+NH_4]^+$.

Step 2. (S)-2-((5-(6-((6-((1,4-Dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

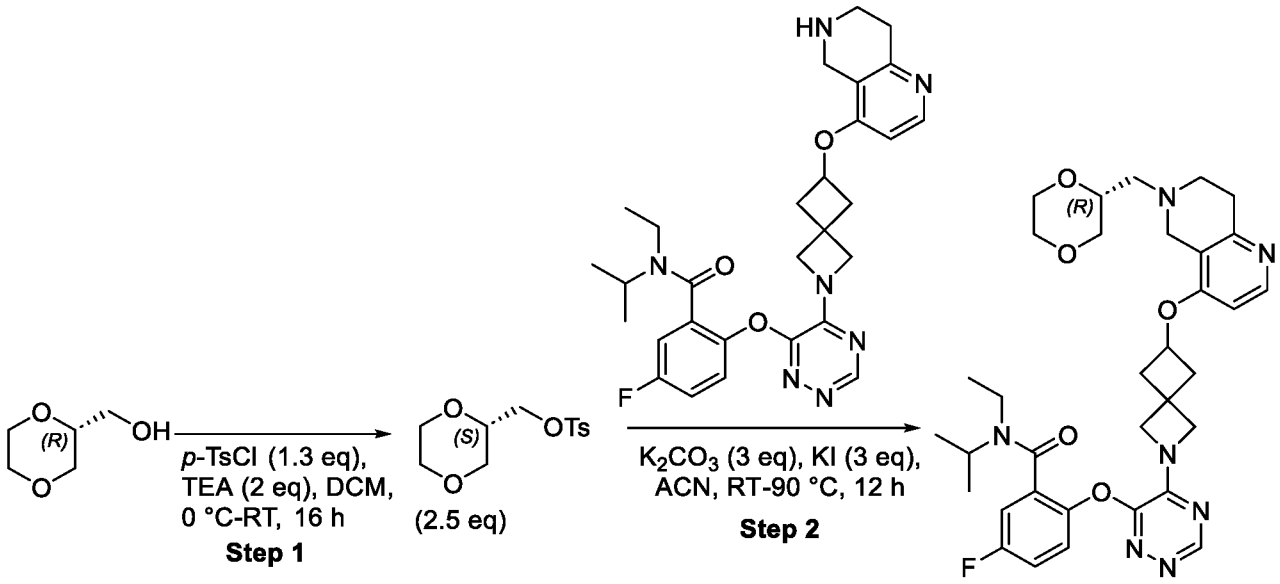


This reaction was performed following the same procedure in two batches (50 mg and 150 mg).

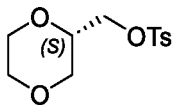
In a 20 mL pressure vial, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (150 mg, 0.274 mmol) was added in ACN (5 mL). To this solution, (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (149 mg, 0.548 mmol), K_2CO_3 (114 mg, 0.822 mmol), and KI (136 mg, 0.822 mmol) were added at RT, and the reaction was stirred at 90 °C for 16 h. The reaction progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with water (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude from both batches were combined and purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*S*)-2-((5-(6-((6-((1,4-dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (54.38 mg, 23.0% combined yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.49 - 7.30 (m, 3H), 6.68 (d, *J* = 5.5 Hz, 1H), 4.79 (quin, *J* = 6.5 Hz, 1H), 4.66 - 4.51 (m, 2H), 4.30 - 4.10 (m, 2H), 3.79 - 3.53 (m, 6H), 3.52 - 3.39 (m, 4H), 3.26 - 2.97 (m, 2H), 2.87 - 2.77 (m, 5H), 2.73 - 2.65 (m, 1H), 2.39 -

2.27 (m, 2H), 1.20 - 0.62 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.63 min, m/z = 648.2 $[M+H]^+$; HPLC (Method G): Rt = 4.85 min, 98.82%; Chira SFC (Method AAF): Rt = 6.53 min, 96.19%.

Example 340. (*R*)-2-((5-(6-((6-((1,4-Dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 369)



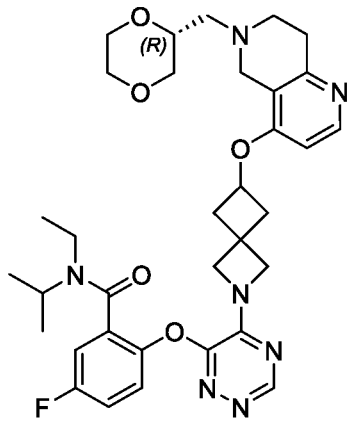
Step 1. (S)-(1,4-Dioxan-2-yl)methyl 4-methylbenzenesulfonate



This compound was synthesized following the procedure described for the synthesis of Example 339, step 1, starting with 1 equivalent of (*R*)-(1,4-dioxan-2-yl)methanol, except that 2 equivalents of TEA was used. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 25% EtOAc in hexane) to obtain (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate as a solid.

Yield: 51.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 4.05 - 3.94 (m, 2H), 3.72 - 3.56 (m, 4H), 3.56 - 3.48 (m, 1H), 3.44 - 3.35 (m, 1H), 3.21 (dd, *J* = 9.9, 11.3 Hz, 1H), 2.43 (s, 3H); LCMS (Method G): Rt = 1.61 min, m/z = 290.0 $[M+NH_4]^+$, 92.74%.

Step 2. (R)-2-((5-(6-((6-((1,4-Dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

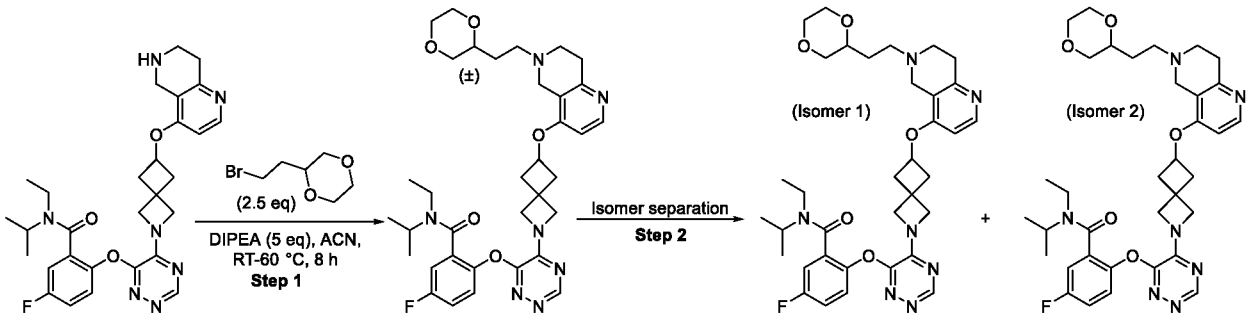


This compound was synthesized following the procedure described for the synthesis of Example 339, step 2, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 2.5 equivalents of (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*R*)-2-((5-(6-((6-((1,4-dioxan-2-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

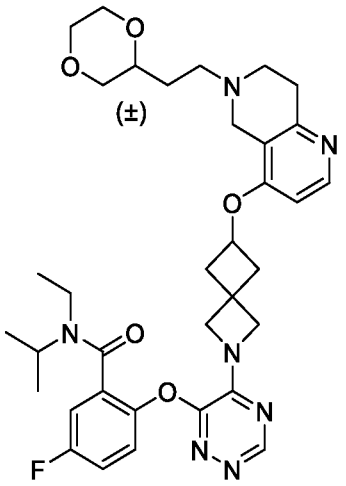
Yield: 30.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.49 - 7.30 (m, 3H), 6.68 (d, *J* = 5.7 Hz, 1H), 4.79 (quin, *J* = 6.5 Hz, 1H), 4.68 - 4.45 (m, 2H), 4.30 - 4.09 (m, 2H), 3.79 - 3.55 (m, 6H), 3.52 - 3.41 (m, 4H), 3.26 - 3.02 (m, 2H), 2.90 - 2.77 (m, 5H), 2.72 - 2.66 (m, 1H), 2.39 - 2.28 (m, 2H), 1.22 - 0.64 (m, 9H)), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.62 min, m/z = 648.2 $[M+H]^+$; HPLC (Method G): Rt = 4.85 min, 99.49%; Chira SFC (Method AAF): Rt = 8.59 min, 98.18%.

Example 341. (*E1*)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 370)

Example 342. (*E2*)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 371)



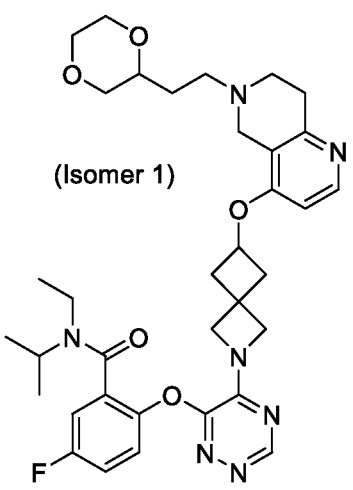
Step 1. (±)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

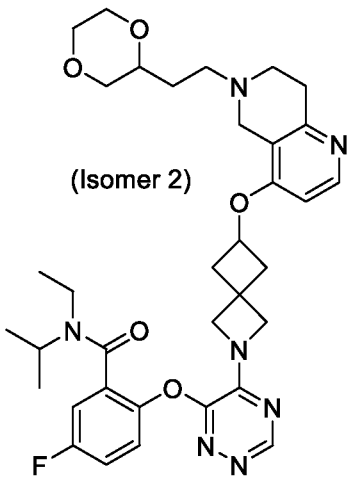


This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 2.5 equivalents of (±)-2-(2-bromoethyl)-1,4-dioxane, except that 5 equivalents of DIPEA was used. The reaction was stirred at 60 °C. After completion, the reaction was cooled to RT and concentrated under reduced pressure. The residue was diluted with water and the mixture was extracted with EtOAc. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate, and filtered, and the filtrate

was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford (±)-2-((5-(6-((6-(2-(1,4-dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid. Yield: 59.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.39 - 7.32 (m, 2H), 6.69 (d, *J* = 5.8 Hz, 1H), 4.83 - 4.75 (m, 1H), 4.66 - 4.49 (m, 2H), 4.33 - 4.13 (m, 2H), 3.75 - 3.67 (m, 2H), 3.65 - 3.59 (m, 2H), 3.58 - 3.49 (m, 2H), 3.47 - 3.40 (m, 4H), 3.23 - 3.15 (m, 1H), 3.13 - 3.01 (m, 1H), 2.87 - 2.81 (m, 4H), 2.76 - 2.62 (m, 2H), 2.39 - 2.30 (m, 2H), 1.62 - 1.52 (m, 2H), 1.18 - 0.92 (m, 7H), 0.76 - 0.67 (m, 2H), two protons merged with solvent peak; LCMS (Method B): Rt = 1.16 min, m/z = 662.5 $[M+H]^+$, 97.28%; Chiral SFC (Method AAE): Peak 1: Rt = 9.01 min, 47.90%; Peak 2: Rt = 10.11 min, 52.10%.

Step 2. (*E1*)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and (*E2*)-2-((5-(6-((6-(2-(1,4-dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide





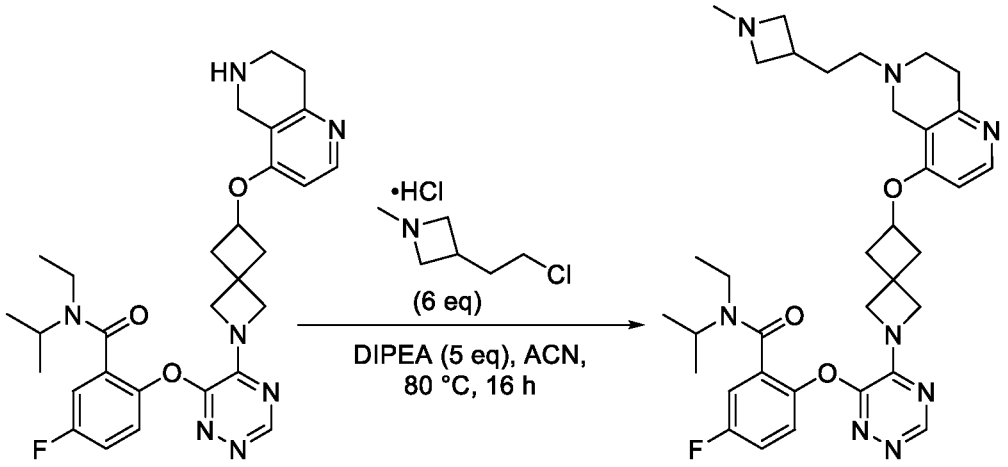
(±)-2-((5-(6-((6-(2-(1,4-Dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (220 mg, 0.332 mmol) was purified using chiral Prep SFC (Method Y) to obtain both isomers,

(*E1*)-2-((5-(6-((6-(2-(1,4-dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (41.95 mg, 18.88% yield) and (*E2*)-2-((5-(6-((6-(2-(1,4-dioxan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (31.82 mg, 14.25%) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.69 (d, J = 5.6 Hz, 1H), 4.83 - 4.75 (m, 1H), 4.65 - 4.50 (m, 2H), 4.32 - 4.10 (m, 2H), 3.74 - 3.67 (m, 2H), 3.65 - 3.60 (m, 2H), 3.58 - 3.49 (m, 2H), 3.48 - 3.40 (m, 4H), 3.23 - 3.14 (m, 1H), 3.12 - 3.00 (m, 1H), 2.87 - 2.80 (m, 4H), 2.75 - 2.63 (m, 2H), 2.38 - 2.32 (m, 2H), 1.60 - 1.50 (m, 2H), 1.15 – 0.93 (m, 7H), 0.75 - 0.68 (m, 2H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.70 min, m/z = 662.4 $[M+H]^+$; HPLC (Method G): Rt = 4.89 min, 98.63%; Chiral SFC (Method AAE): Rt = 9.21 min, 100%.

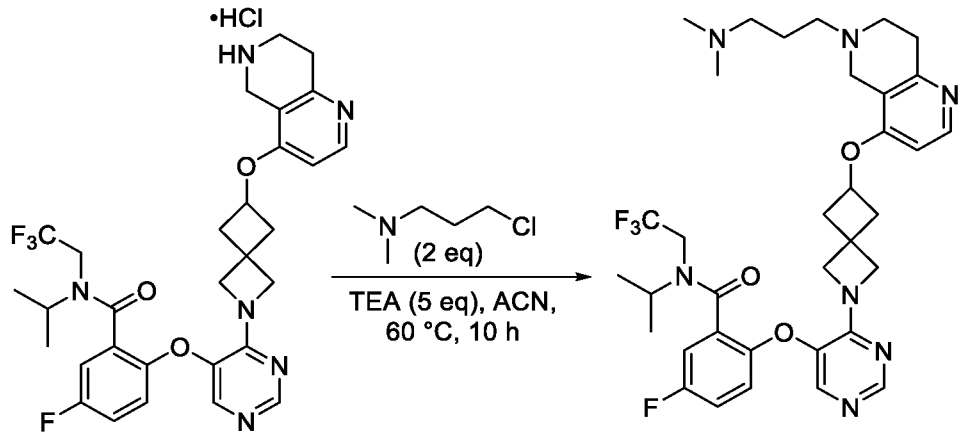
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ; 8.47 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.69 (d, J = 5.7 Hz, 1H), 4.83 - 4.75 (m, 1H), 4.66 - 4.50 (m, 2H), 4.33 - 4.11 (m, 2H), 3.75 - 3.67 (m, 2H), 3.66 - 3.60 (m, 2H), 3.58 - 3.49 (m, 2H), 3.48 - 3.39 (m, 4H), 3.24 - 3.14 (m, 1H), 3.14 - 2.99 (m, 1H), 2.88 - 2.79 (m, 4H), 2.74 - 2.63 (m, 2H), 2.39 - 2.29 (m, 2H), 1.61 - 1.51 (m, 2H), 1.15 - 0.92 (m, 7H), 0.75 - 0.67 (m, 2H), two protons merged with solvent peak; LCMS (Method G): Rt = 1.71 min, m/z = 662.4 $[M+H]^+$; HPLC (Method G): Rt = 4.88 min, 99.49%; Chiral SFC (Method AAE): Rt = 10.46 min, 100%.

Example 343. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 325)



This compound was synthesized following the procedure described for the synthesis of Example 136, step 3, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and 6 equivalents of 3-(2-chloroethyl)-1-methylazetidine hydrochloride. The reaction was stirred at 80 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(2-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.
Yield: 3.48%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.68 (d, *J* = 5.8 Hz, 1H), 4.82 - 4.74 (m, 1H), 4.66 - 4.49 (m, 2H), 4.26 - 4.12 (m, 2H), 3.68 - 3.57 (m, 1H), 3.43 (d, *J* = 6.1 Hz, 2H), 3.14 - 2.99 (m, 2H), 2.86 - 2.76 (m, 5H), 2.75 - 2.70 (m, 1H), 2.45 - 2.37 (m, 6H), 2.22 (s, 3H), 1.89 - 1.82 (m, 1H), 1.45 - 1.35 (m, 1H), 1.16 - 0.93 (m, 7H), 0.75 - 0.68 (m, 2H), three protons merged with solvent peak; LCMS (Method G): Rt = 1.74 min, m/z = 645.3 $[M+H]^+$; HPLC (Method A): Rt = 4.34 min, 98.59%.

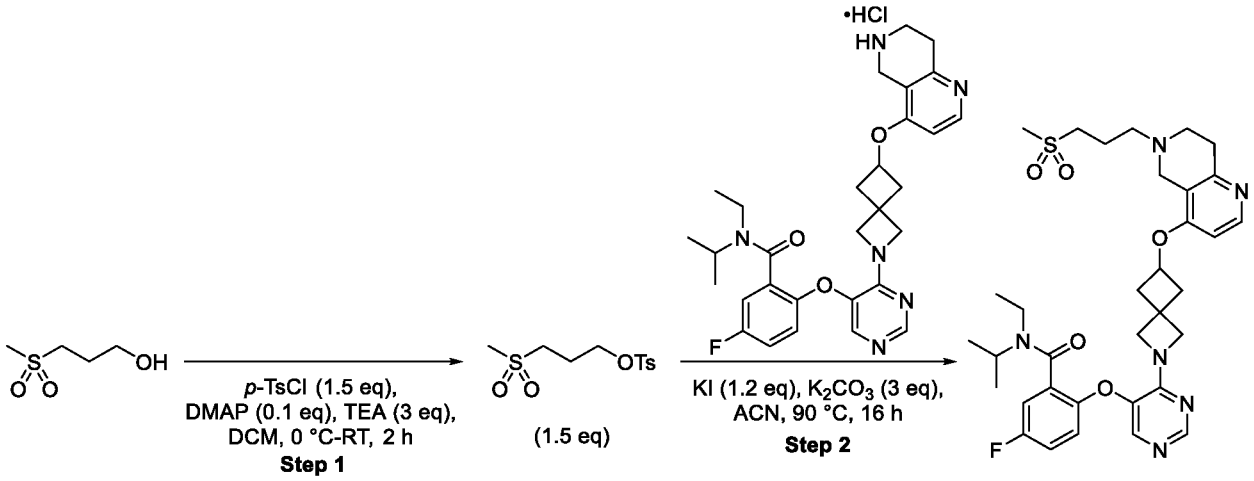
Example 344. 2-((4-(6-((6-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 372)



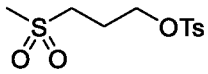
This compound was synthesized following the procedure described for the synthesis of Example 14, starting with 1 equivalent of 5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride and 2 equivalents of 3-chloro-*N*,*N*-dimethylpropan-1-amine, except that 5 equivalents of TEA was used. The reaction was stirred at 60 °C. The crude was purified by achiral Prep SFC (Method S) to afford 2-((4-(6-((6-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 39.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.17 (d, *J* = 5.7 Hz, 1H), 7.79 (s, 1H), 7.37 - 7.23 (m, 2H), 7.03 (dd, *J* = 4.3, 8.9 Hz, 1H), 6.65 (d, *J* = 5.7 Hz, 1H), 4.73 (quin, *J* = 6.5 Hz, 1H), 4.39 - 4.04 (m, 6H), 4.01 - 3.85 (m, 1H), 3.45 – 3.39 (m, 3H), 2.85 - 2.72 (m, 5H), 2.71 - 2.64 (m, 2H), 2.31 - 2.19 (m, 4H), 2.12 (s, 6H), 1.62 (quin, *J* = 7.2 Hz, 2H), 1.36 - 1.04 (m, 6H); LCMS (Method A): Rt = 2.45 min, m/z = 686.3 $[M+H]^+$; HPLC (Method A): Rt = 5.17 min, 99.70%.

Example 345. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 373)

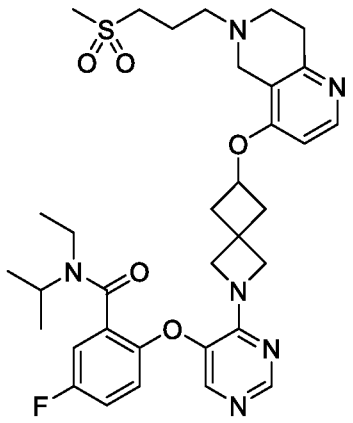


Step 1. 3-(Methylsulfonyl)propyl 4-methylbenzenesulfonate



This compound was synthesized following the procedure described for the synthesis of Intermediate 42, starting with 1.5 equivalents of *p*-TsCl, except that 1 equivalent of 3-(methylsulfonyl)propan-1-ol and 0.1 equivalent of DMAP were used. After completion, saturated $NaHCO_3$ was added to the reaction and the mixture was extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (product was eluted at 60% EtOAc in hexane) to obtain 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate as a solid. Yield: 60.7%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.20 (t, *J* = 5.9 Hz, 2H), 3.18 - 3.08 (m, 2H), 2.93 (s, 3H), 2.48 (s, 3H), 2.30 - 2.20 (m, 2H).

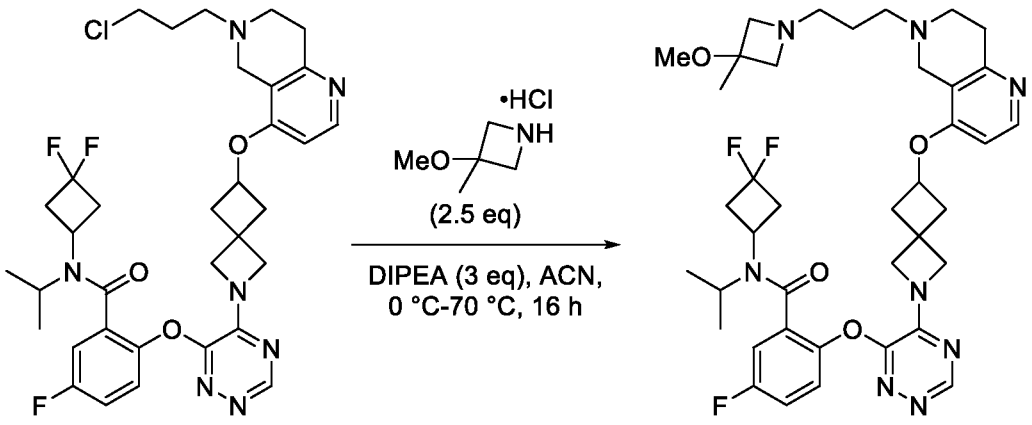
Step 2. N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 147, step 1, starting with *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride, except that 1.5 equivalents of 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate, 1.2 equivalents of KI, and 3 equivalents of K_2CO_3 were used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with ACN. The filtrate was concentrated under reduced pressure. EtOAc was added to the residue and the mixture was washed with 10% $NaHCO_3$ solution. The combined organic layer was dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The obtained product was impure. Therefore, the product was re-purified by Prep HPLC (Method D) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

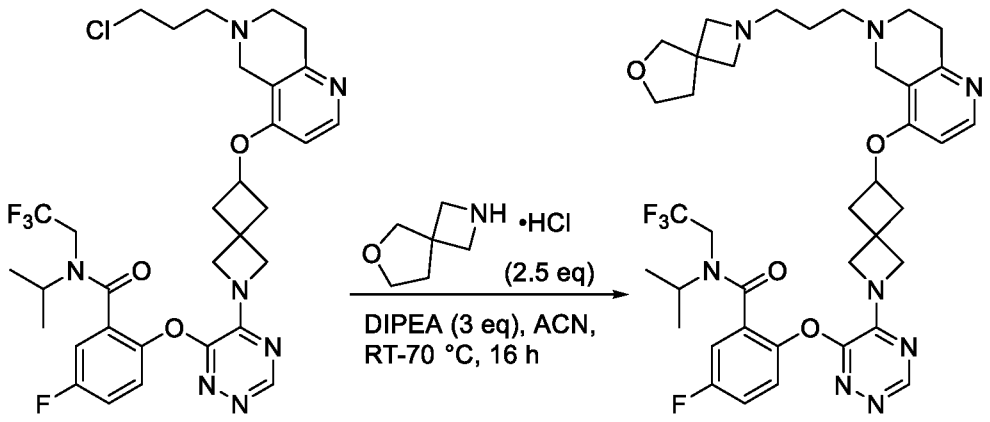
Yield: 8.20%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.71 - 6.65 (m, 1H), 4.81 - 4.67 (m, 1H), 4.33 - 4.05 (m, 3H), 3.76 (spt, J = 6.6 Hz, 1H), 3.45 (s, 2H), 3.42 - 3.36 (m, 1H), 3.28 - 3.20 (m, 1H), 3.19 - 3.10 (m, 2H), 2.98 (s,3H), 2.86 - 2.74 (m, 5H), 2.73 - 2.67 (m, 2H), 2.61 (t, J = 6.8 Hz, 2H), 2.31 - 2.22 (m, 2H), 2.00 - 1.85 (m, 2H), 1.31 - 0.91 (m, 9H); LCMS (Method G): Rt = 1.70 min, m/z = 667.3 $[M+H]^+$; HPLC (Method G): Rt = 4.82 min, 99.94%.

Example 346. ***N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide** (Compound No. 312)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2.5 equivalents of 3-methoxy-3-methylazetidine hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford the product. The product was impure and therefore, it was re-purified by achiral Prep SFC (Method Q) to afford *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(3-(3-methoxy-3-methylazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid. Yield: 26.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.52 - 7.34 (m, 3H), 6.68 (br s, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.70 - 4.45 (m, 2H), 4.31 - 4.10 (m, 2H), 3.93 - 3.79 (m, 1H), 3.75 - 3.55 (m, 2H), 3.40 (br s, 3H), 3.14 - 3.05 (m, 5H), 2.91 - 2.76 (m, 7H), 2.72 - 2.62 (m, 4H), 2.44 - 2.25 (m, 5H), 1.58 - 1.45 (m, 2H), 1.36 (s, 3H), 1.19 - 1.00 (m, 3H), 0.94 - 0.53 (m, 3H); LCMS (Method G): Rt = 1.92 min, m/z = 751.7 $[M+H]^+$; HPLC (Method A): Rt = 5.27 min, 99.15%.

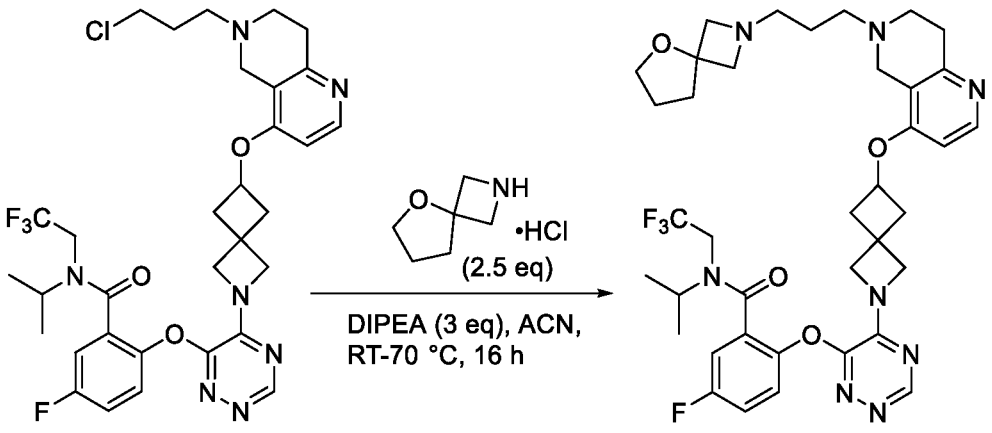
Example 347. 2-((5-(6-((6-(3-(6-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 323)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 2.5 equivalents of 6-oxa-2-azaspiro[3.4]octane hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 26.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 - 8.41 (m, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.53 - 7.38 (m, 3H), 6.68 (br d, J = 5.1 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.64 - 4.42 (m, 2H), 4.34 - 3.97 (m, 4H), 3.83 - 3.73 (m, 1H), 3.67 (s, 2H), 3.63 (t, J = 6.9 Hz, 2H), 3.40 (br s, 2H), 3.06 (br s, 4H), 2.83 - 2.79 (m, 4H), 2.67 - 2.65 (m, 2H), 2.46 - 2.34 (m, 4H), 1.97 (br t, J = 6.8 Hz, 2H), 1.49 (br s, 2H), 1.16 - 0.66 (m, 6H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.80 min, m/z = 755.4 $[M+H]^+$; HPLC (Method A): Rt = 5.01 min, 98.58%.

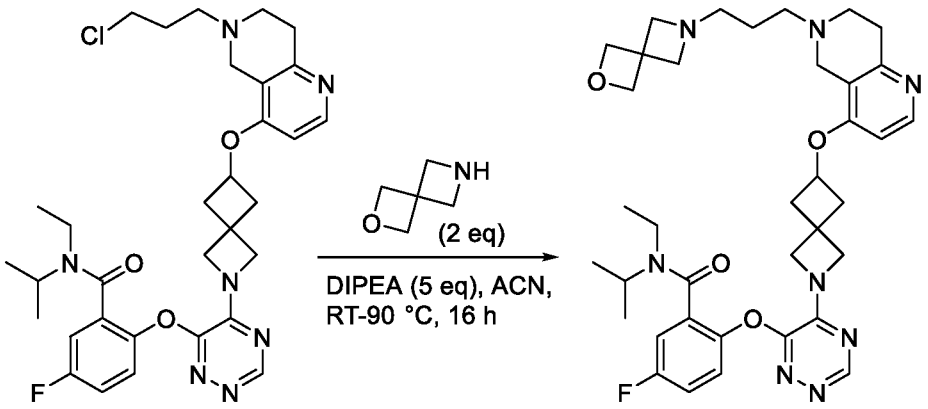
Example 348. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 324)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 2.5 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C in a pressure vial. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by Prep HPLC (Method B). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 19.08%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (m, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.51 - 7.38 (m, 3H), 6.68 (br d, J = 4.9 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.67 - 4.42 (m, 2H), 4.38 - 3.99 (m, 4H), 3.85 - 3.72 (m, 1H), 3.65 (t, J = 6.7 Hz, 2H), 3.40 (br s, 2H), 3.27 - 3.16 (m, 2H), 2.92 - 2.75 (m, 6H), 2.68 - 2.63 (m, 2H), 2.46 - 2.29 (m, 4H), 1.98 (br t, J = 7.0 Hz, 2H), 1.80 (quin, J = 6.9 Hz, 2H), 1.50 (br s, 2H), 1.13 - 0.68 (m, 6H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.91 min, m/z = 755.6 $[M+H]^+$; HPLC (Method A): Rt = 5.16 min, 98.95%.

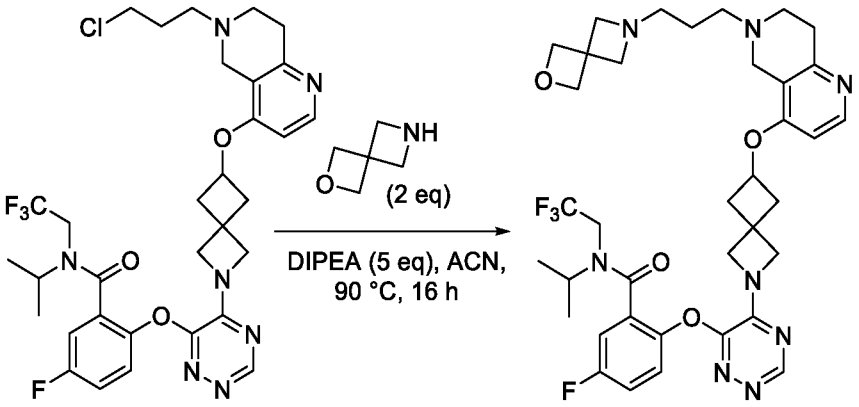
Example 349. 2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 332)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 2-oxa-6-azaspiro[3.3]heptane. The reaction was stirred at 90 °C in a pressure vial. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by Prep HPLC (Method AM). The product fractions were concentrated under reduced pressure and lyophilized to afford 2-((5-(6-((6-(3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 10.45%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.48 - 7.32 (m, 3H), 6.68 (d, J = 5.8 Hz, 1H), 4.78 (quin, J = 6.7 Hz, 1H), 4.65 - 4.49 (m, 6H), 4.26 - 4.11 (m, 2H), 3.68 - 3.56 (m, 1H), 3.39 (s, 2H), 3.21 (br s, 4H), 3.15 - 3.01 (m, 1H), 2.86 - 2.76 (m, 5H), 2.64 - 2.61 (m, 2H), 2.47 - 2.41 (m, 2H), 2.32 - 2.26 (m, 2H), 1.46 (br s, 2H), 1.15 - 0.67 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.62 min, m/z = 687.6 $[M+H]^+$; HPLC (Method A): Rt = 4.50 min, 99.58%.

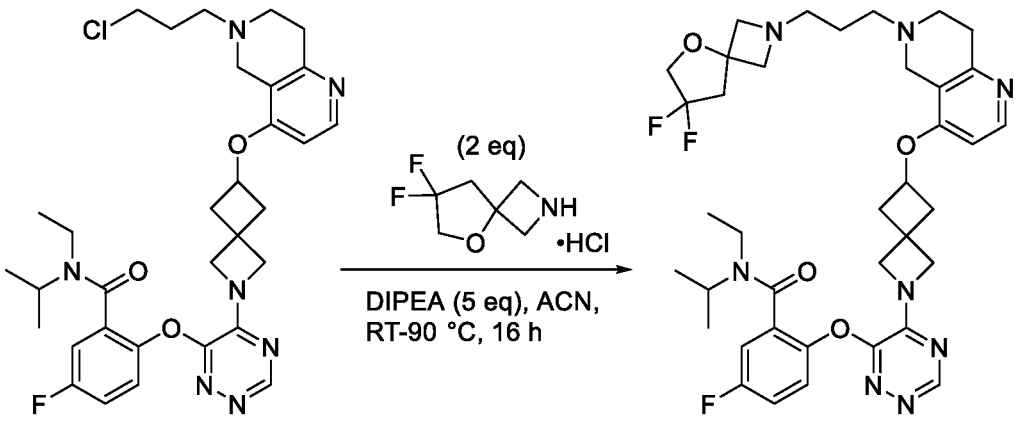
Example 350. 2-((5-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 374)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 2 equivalents of 2-oxa-6-azaspiro[3.3]heptane. The reaction was stirred at 90 °C. After completion, the reaction was concentrated under reduced pressure and the crude was purified by Prep HPLC (Method AO) to obtain 2-((5-(6-((6-(3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 32.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.56 - 7.37 (m, 3H), 6.68 (br d, J = 5.0 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.58 (s, 4H), 4.56 - 4.44 (m, 2H), 4.40 - 3.86 (m, 4H), 3.84 - 3.66 (m, 1H), 3.39 (br s, 2H), 3.21 (br s, 4H), 2.88 - 2.74 (m, 4H), 2.71 - 2.61 (m, 2H), 2.48 - 2.40 (m, 2H), 2.38 - 2.23 (m, 4H), 1.54 - 1.37 (m, 2H), 1.30 - 0.97 (m, 3H), 0.84 - 0.61 (m, 3H); LCMS (Method G): Rt = 1.69 min, m/z = 741.3 $[M+H]^+$; HPLC (Method G): Rt = 4.81 min, 99.80%.

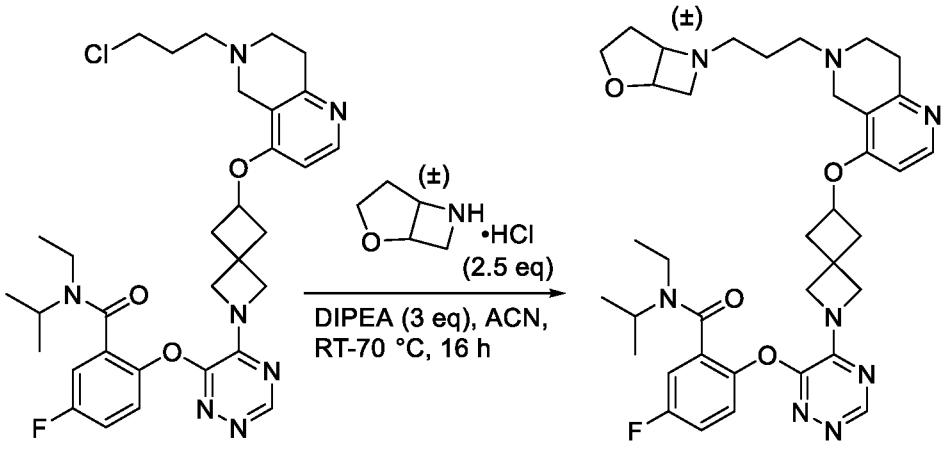
Example 351. 2-((5-(6-((6-(3-(7,7-Difluoro-5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 375)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 7,7-difluoro-5-oxa-2-azaspiro[3.4]octane hydrochloride. The reaction was stirred at 90 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((5-(6-((6-(3-(7,7-difluoro-5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 19.94%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.68 (d, J = 5.8 Hz, 1H), 4.82 - 4.74 (m, 1H), 4.68 - 4.46 (m, 2H), 4.34 - 4.10 (m, 2H), 3.94 (t, J = 13.1 Hz, 2H), 3.68 - 3.57 (m, 1H), 3.41 - 3.35 (m, 4H), 3.14 - 3.00 (m, 3H), 2.87 - 2.76 (m, 4H), 2.70 - 2.59 (m, 4H), 2.47 - 2.35 (m, 4H), 1.50 (br s, 2H), 1.15 - 0.67 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.67 min, m/z = 737.3 $[M+H]^+$; HPLC (Method G): Rt = 5.26 min, 99.11%.

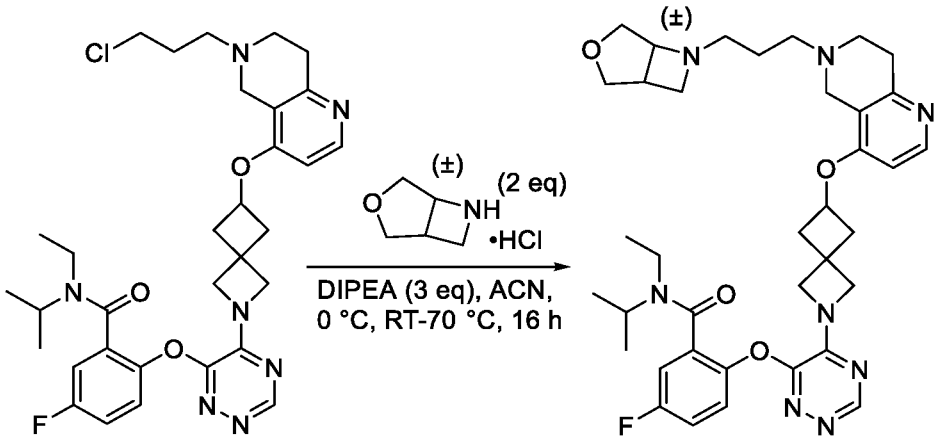
Example 352. (±)-2-((5-(6-((6-(3-(2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 376)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2.5 equivalents of (±)-2-oxa-6-azabicyclo[3.2.0]heptane, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C in a pressure vial. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (±)-2-((5-(6-((6-(3-(2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide as a solid.

Yield: 32.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.68 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.69 - 4.48 (m, 3H), 4.33 - 4.11 (m, 2H), 4.10 - 4.03 (m, 1H), 4.02 - 3.94 (m, 1H), 3.82 (br s, 1H), 3.68 - 3.58 (m, 1H), 3.41 (s, 2H), 3.19 - 2.96 (m, 4H), 2.85 - 2.76 (m, 4H), 2.68 - 2.60 (m, 2H), 2.38 - 2.26 (m, 2H), 1.78 - 1.72 (m, 1H), 1.56 - 1.41 (m, 3H), 1.17 - 0.66 (m, 9H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.61 min, m/z = 687.2 $[M+H]^+$; HPLC (Method A): Rt = 4.67 min, 99.55%.

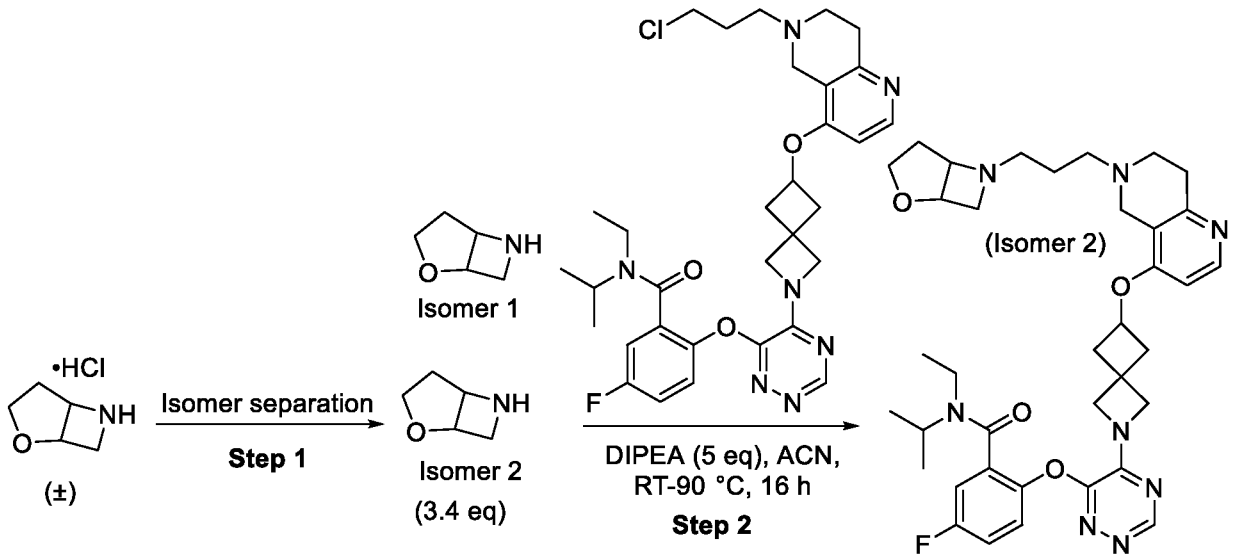
Example 353. (±)-2-((5-(6-((6-(3-(3-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 377)



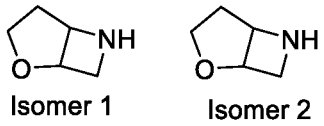
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of (±)-3-oxa-6-azabicyclo[3.2.0]heptane hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (±)-2-((5-(6-((6-(3-(3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 13.32%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.22 - 8.17 (m, 1H), 7.49 - 7.32 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.64 - 4.48 (m, 2H), 4.32 - 4.10 (m, 2H), 3.85 - 3.76 (m, 3H), 3.68 - 3.57 (m, 1H), 3.42 - 3.37 (m, 3H), 3.19 - 2.92 (m, 6H), 2.86 - 2.76 (m, 4H), 2.68 - 2.65 (m, 1H), 2.49 -2.40 (m, 3H), 2.35 - 2.31 (m, 2H), 1.45 (br s, 2H), 1.17 - 0.66 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.61 min, m/z = 687.2 $[M+H]^+$; HPLC (Method A): Rt = 4.53 min, 99.69%.

Example 354. ***(E2)*-2-((5-(6-((6-(3-(2-Oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide** (Compound No. 378)



Step 1. (E1)-2-Oxa-6-azabicyclo[3.2.0]heptane and (E2)-2-oxa-6-azabicyclo[3.2.0]heptane

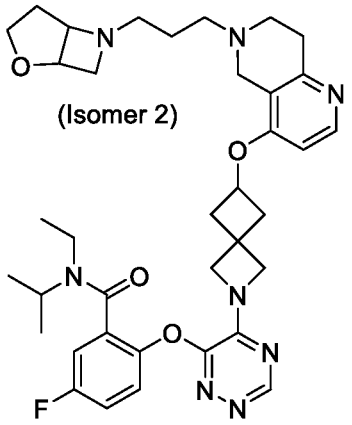


(±)-2-Oxa-6-azabicyclo[3.2.0]heptane hydrochloride (0.5 g, 3.69 mmol) was purified by chiral Prep SFC (Method AI) and the product fractions were concentrated under reduced pressure to obtain both isomers, (*E1*)-2-oxa-6-azabicyclo[3.2.0]heptane (0.05 g, 13.68% yield) and (*E2*)-2-oxa-6-azabicyclo[3.2.0]heptane (0.05 g, 13.68% yield) as gummy liquids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.75 - 4.67 (m, 1H), 4.36 (br t, J = 5.0 Hz, 1H), 4.14 - 4.00 (m, 2H), 3.62 (br dd, J = 5.8, 10.0 Hz, 1H), 3.16 (br dd, J = 1.8, 10.0 Hz, 1H), 1.75 (dd, J = 4.7, 12.6 Hz, 1H), 1.59 - 1.46 (m, 1H), one proton merged with solvent peaks.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.75 - 4.64 (m, 1H), 4.34 (br t, J = 4.9 Hz, 1H), 4.13 - 3.99 (m, 2H), 3.61 (br dd, J = 5.8, 9.7 Hz, 1H), 3.14 (br d, J = 9.9 Hz, 1H), 1.73 (br dd, J = 4.5, 12.5 Hz, 1H), 1.56 - 1.41 (m, 1H), one proton merged with solvent peaks.

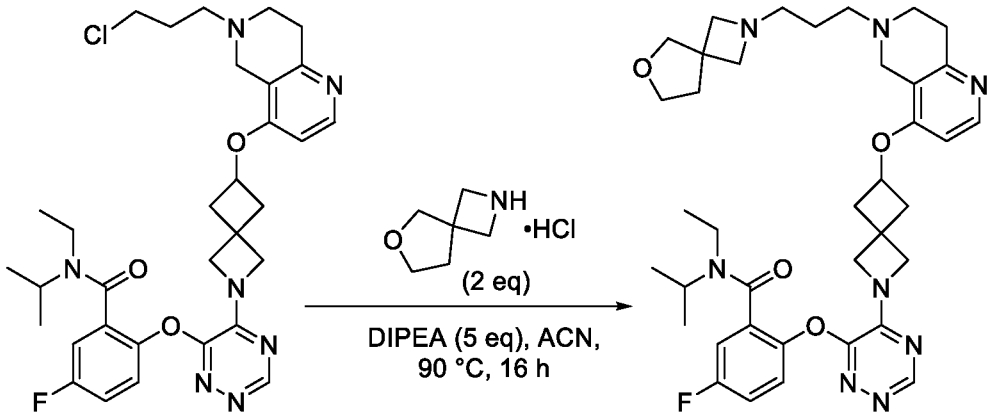
Step 2. (E2)-2-((5-(6-((6-(3-(2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 3.4 equivalents of (*E2*)-2-oxa-6-azabicyclo[3.2.0]heptane. The reaction was stirred at 90 °C in a pressure vial. The reaction was diluted saturated aqueous sodium bicarbonate solution and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by Prep HPLC (Method AQ). The product fractions were concentrated under reduced pressure and lyophilized to afford *(E2)*-2-((5-(6-((6-(3-(2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 7.63%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.49 - 7.28 (m, 3H), 6.68 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.66 - 4.49 (m, 3H), 4.32 - 4.12 (m, 2H), 4.10 - 4.03 (m, 1H), 4.02 - 3.93 (m, 1H), 3.82 (br s, 1H), 3.66 - 3.57 (m, 1H), 3.41 (s, 2H), 3.16 - 3.00 (m, 4H), 2.83 - 2.69 (m, 4H), 2.68 - 2.64 (m, 2H), 2.35 - 2.27 (m, 2H), 1.79 - 1.71 (m, 1H), 1.55 - 1.42 (m, 3H), 1.16 - 0.68 (m, 9H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.67 min, m/z = 687.3 $[M+H]^+$; HPLC (Method G): Rt = 4.63 min, 94.37%. Chiral SFC (Method AAN): Rt = 4.02 min, 100%.

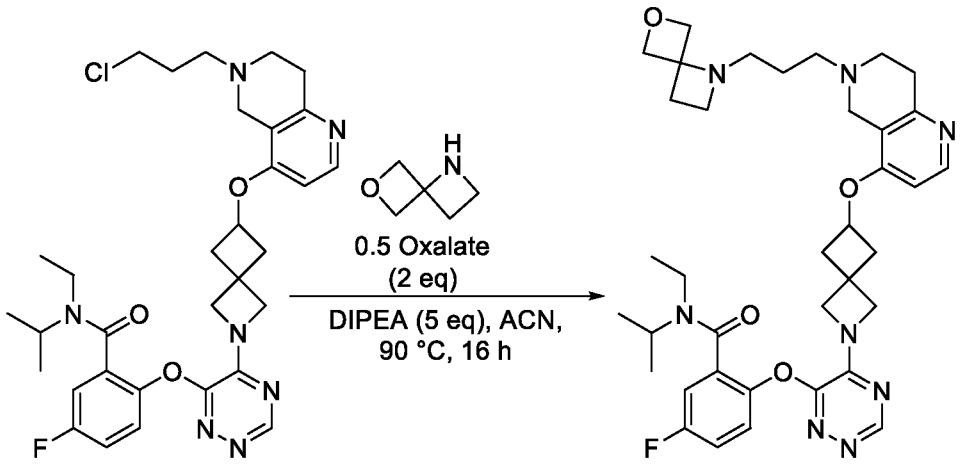
Example 355. 2-((5-(6-((6-(3-(6-Oxa-2-Azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 322)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 6-oxa-2-azaspiro[3.4]octane hydrochloride. The reaction was stirred at 90 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((5-(6-((6-(3-(6-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 17.54%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 6.68 (d, J = 5.6 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.66 - 4.49 (m, 2H), 4.33 - 4.12 (m, 2H), 3.69 - 3.66 (m, 2H), 3.63 (t, J = 6.9 Hz, 2H), 3.40 (br s, 2H), 3.06 (br s, 5H), 2.87 - 2.76 (m, 4H), 2.69 - 2.65 (m, 2H), 2.48-2.35 (m, 4H), 1.97 (t, J = 6.8 Hz, 2H), 1.54-1.42 (m, 2H), 1.16 - 0.92 (m, 7H), 0.77-0.66 (m, 2H), four protons merged with solvent peak; LCMS (Method G): Rt = 1.66 min, m/z = 701.7 $[M+H]^+$; HPLC (Method D): Rt = 2.05 min, 97.51%.

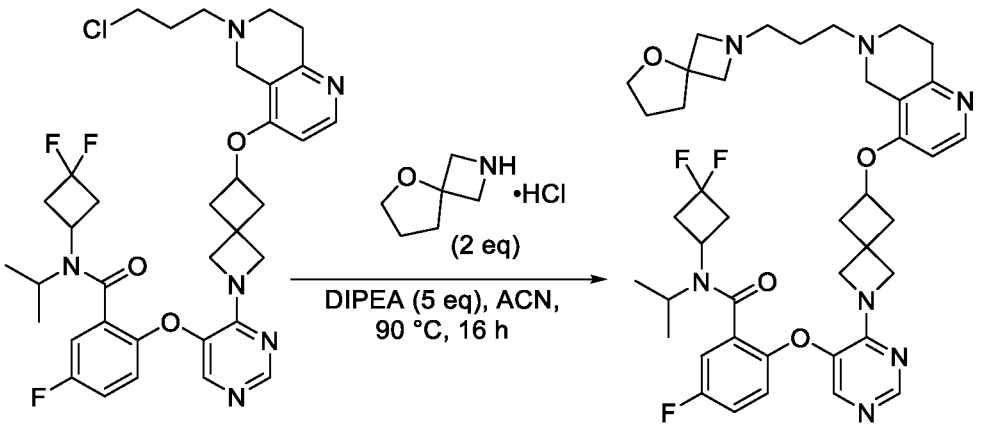
Example 356. 2-((5-(6-((6-(3-(6-Oxa-1-azaspiro[3.3]heptan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 379)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 6-oxa-1-azaspiro[3.3]heptane oxalate. The reaction was stirred at 90 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by achiral Prep SFC (Method P) to afford 2-((5-(6-((6-(3-(6-oxa-1-azaspiro[3.3]heptan-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 9.93%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 - 7.32 (m, 2H), 6.69 (d, J = 5.7 Hz, 1H), 4.83 - 4.74 (m, 3H), 4.66 - 4.51 (m, 2H), 4.51 - 4.45 (m, 2H), 4.33 - 4.12 (m, 2H), 3.67 - 3.57 (m, 1H), 3.43 (br s, 2H), 3.15 - 3.01 (m, 1H), 3.00 - 2.93 (m, 2H), 2.88 - 2.77 (m, 4H), 2.73 - 2.68 (m, 2H), 2.65 - 2.58 (m, 2H), 2.39 - 2.28 (m, 2H), 2.26 - 2.20 (m, 2H), 1.67 - 1.57 (m, 2H), 1.16 - 0.92 (m, 7H), 0.75 - 0.68 (m, 2H), three protons merged with solvent peak; LCMS (Method G): Rt = 1.59 min, m/z = 687.3 $[M+H]^+$; HPLC (Method G): Rt = 4.63 min, 97.53%.

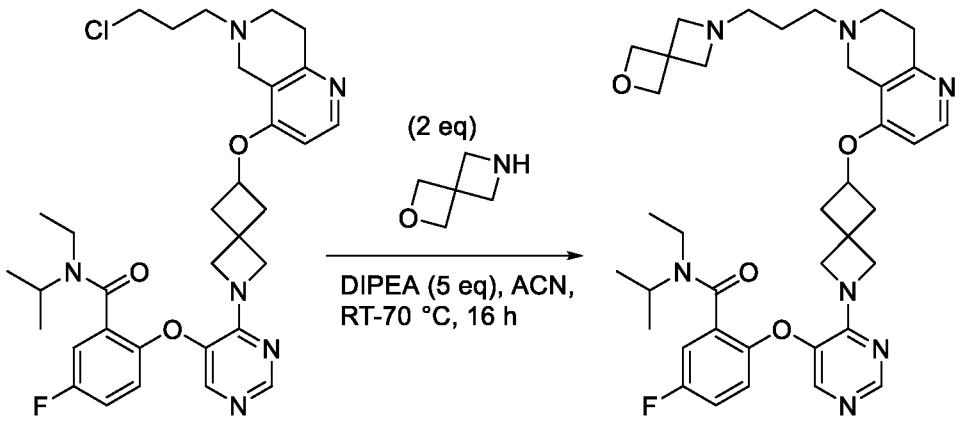
Example 357. 2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 380)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride. The reaction was stirred at 90 °C. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 6.91%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.33 (m, 1H), 7.31 - 7.24 (m, 1H), 7.09 - 7.03 (m, 1H), 6.65 (d, *J* = 5.6 Hz, 1H), 4.78 - 4.69 (m, 1H), 4.31 - 4.07 (m, 4H), 3.97 - 3.86 (m, 1H), 3.78 - 3.70 (m, 2H), 3.65 (t, *J* = 6.7 Hz, 2H), 3.61-3.49 (m, 1H), 3.40 (br s, 2H), 3.24 (d, *J* = 7.9 Hz, 2H), 2.88 (d, *J* = 7.9 Hz, 2H), 2.82 - 2.74 (m, 5H), 2.69 - 2.64 (m, 3H), 2.48 - 2.44 (m, 2H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.26 (dd, *J* = 6.4, 12.9 Hz, 2H), 2.01 - 1.94 (m, 2H), 1.84 - 1.76 (m, 2H), 1.54 - 1.45 (m, 2H), 1.13 - 0.99 (m, 6H); LCMS (Method G): Rt = 1.92 min, m/z = 762.4 $[M+H]^+$; HPLC (Method A): Rt = 5.61 min, 99.72%.

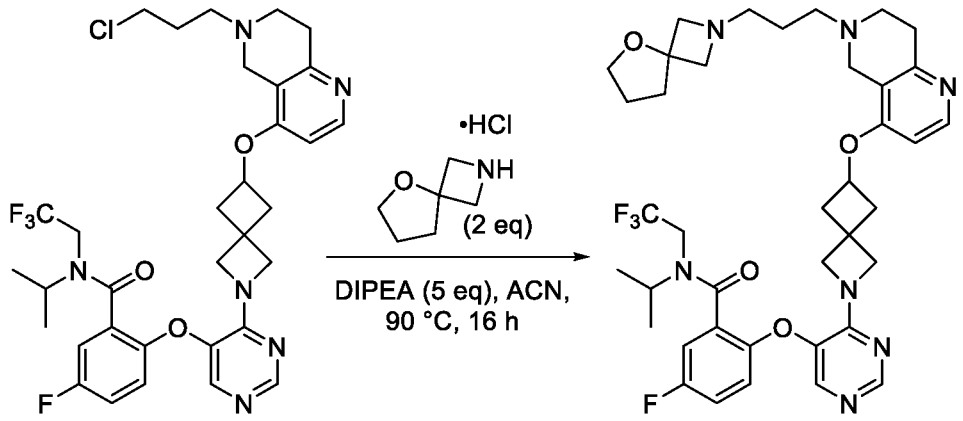
Example 358. 2-((4-(6-((6-(3-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 381)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 2-oxa-6-azaspiro[3.3]heptane was used. The reaction was stirred at 70 °C. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((4-(6-((6-(3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 29.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.70 - 6.61 (m, 1H), 4.79 - 4.69 (m, 1H), 4.58 (s, 4H), 4.47 - 4.06 (m, 4H), 3.82 - 3.66 (m, 1H), 3.46 - 3.36 (m, 3H), 3.30 - 3.23 (m, 1H), 3.21 (s, 4H), 2.83 - 2.74 (m, 4H), 2.67 - 2.60 (m, 2H), 2.45 (br t, J = 7.2 Hz, 2H), 2.35 - 2.22 (m, 4H), 1.46 (quin, J = 7.1 Hz, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.71 min, m/z = 686.3 $[M+H]^+$; HPLC (Method G): Rt = 4.65 min, 99.06%.

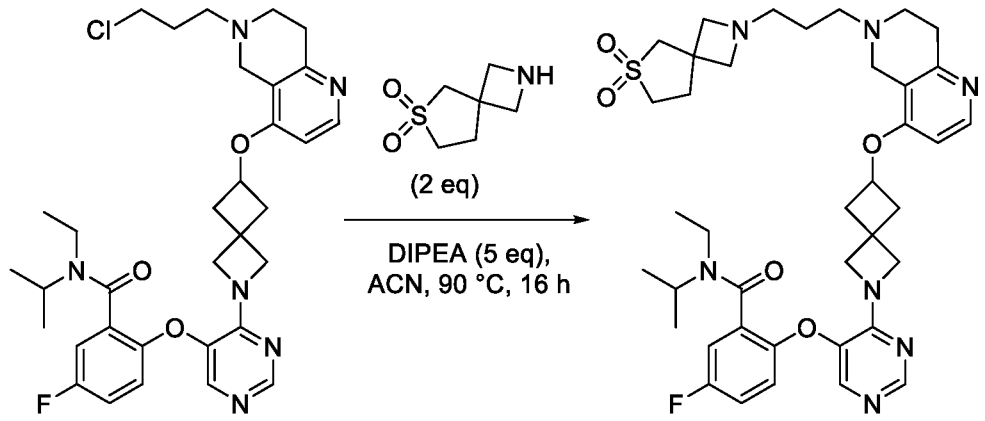
Example 359. 2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 382)



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide and 2 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride. The reaction was stirred at 90 °C. After completion, water was added to the reaction, and the mixture was extracted with EtOAc. The combined organic layer was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

Yield: 39.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.39 - 7.23 (m, 2H), 7.03 (dd, J = 4.3, 8.9 Hz, 1H), 6.65 (d, J = 5.8 Hz, 1H), 4.73 (quin, J = 6.5 Hz, 1H), 4.38 - 4.02 (m, 5H), 4.00 - 3.87 (m, 1H), 3.65 (t, J = 6.8 Hz, 2H), 3.38 (s, 2H), 3.27 - 3.20 (m, 2H), 2.88 (d, J = 7.9 Hz, 2H), 2.83 - 2.72 (m, 4H), 2.71 - 2.62 (m, 2H), 2.49 - 2.43 (m, 3H), 2.39 (br t, J = 7.1 Hz, 2H), 2.30 - 2.18 (m, 2H), 2.02 - 1.93 (m, 2H), 1.80 (quin, J = 6.9 Hz, 2H), 1.49 (quin, J = 7.0 Hz, 2H), 1.11 (br t, J = 7.6 Hz, 6H); LCMS (Method B): Rt = 1.08 min, m/z = 754.2 $[M+H]^+$; HPLC (Method A): Rt = 5.48 min, 98.32%.

Example 360. 2-((4-(6-((6-(3-(6,6-Dioxido-6-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 383)

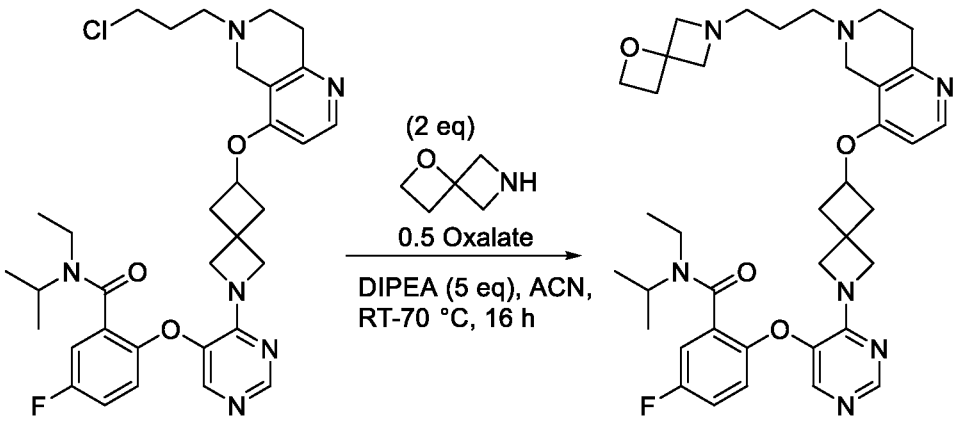


This reaction was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents 6-thia-2-azaspiro[3.4]octane 6,6-dioxide was used. The reaction was stirred at 90 °C. The crude from both batches were combined and purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-(3-(6,6-dioxido-6-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Combined yield: 38.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.20 - 8.15 (m, 1H), 7.76 – 7.67 (m, 1H), 7.34 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.69 - 6.64 (m, 1H), 4.78 - 4.69 (m, 1H), 4.30 - 4.07 (m, 4H), 3.82 - 3.70 (m, 1H), 3.45 - 3.37 (m, 4H), 3.27 - 3.23 (m, 3H), 3.16 - 3.08 (m, 6H), 2.84 - 2.74 (m, 4H), 2.67 - 2.62 (m, 2H), 2.44 - 2.37 (m, 3H), 2.32 - 2.22 (m, 4H), 1.55 - 1.43 (m, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.67 min, m/z = 748.4 $[M+H]^+$; HPLC (Method G): Rt = 4.76 min, 99.88%.

Example 361. 2-((4-(6-((6-(3-(1-Oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 384)

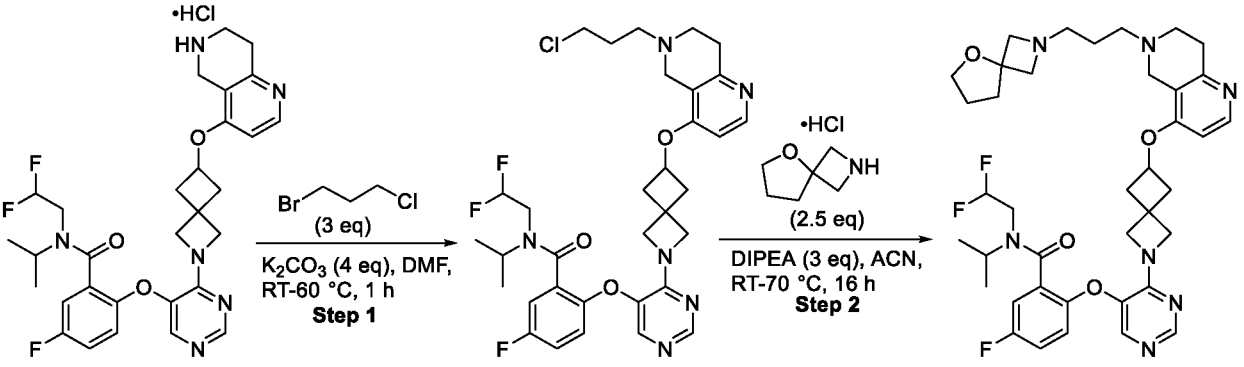


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of 1-oxa-6-azaspiro[3.3]heptane oxalate was used. The reaction was stirred at 70 °C.

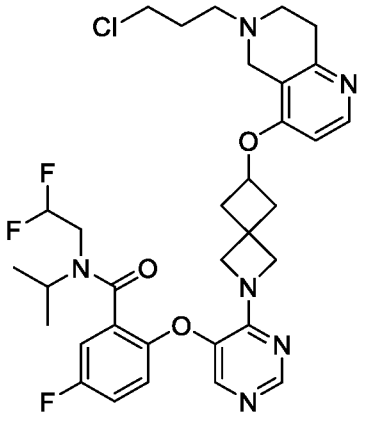
The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by Prep HPLC (Method H). The isolated compound showed an acetic acid peak in the ^{1}HNMR spectrum. Therefore, the product was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 2-((4-(6-((6-(3-(1-oxa-6-azaspiro[3.3]heptan-6-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 5.29%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.76 - 7.64 (m, 1H), 7.34 - 7.19 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.62 (m, 1H), 4.80 - 4.69 (m, 1H), 4.36 (t, J = 7.6 Hz, 2H), 4.31 - 4.07 (m, 4H), 3.81 - 3.67 (m, 1H), 3.50 - 3.45 (m, 2H), 3.43 - 3.36 (m, 3H), 3.27 - 3.09 (m, 2H), 2.97 - 2.91 (m, 2H), 2.83 - 2.70 (m, 5H), 2.67 - 2.60 (m, 2H), 2.48 - 2.43 (m, 2H), 2.38 - 2.32 (m, 2H), 2.31 - 2.22 (m, 2H), 1.48 (quin, J = 7.1 Hz, 2H), 1.26 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.71 min, m/z = 686.4 $[M+H]^+$; HPLC (Method G): Rt = 4.75 min, 98.39%.

Example 362. 2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 338)



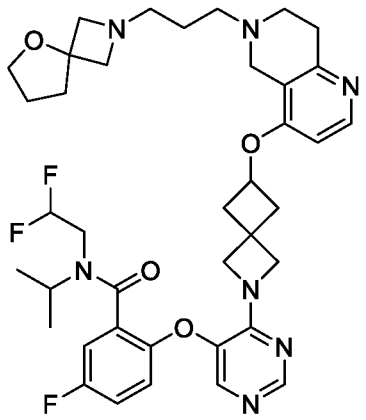
Step 1. 2-((4-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalents of 1-bromo-3-chloropropane, except that 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride was used, to afford crude 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid. The reaction was stirred in a pressure vial. This material was used without further purification.

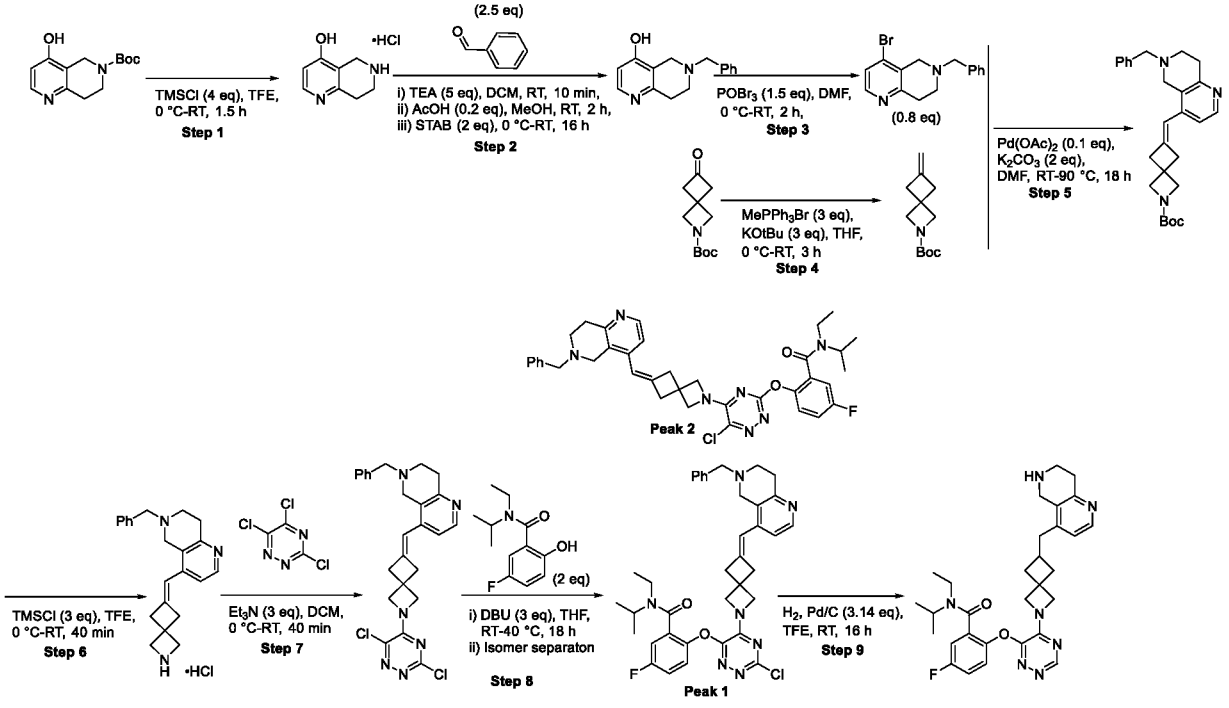
Yield: 76%; LCMS (Method G): Rt = 2.12 min, m/z = 659.5 $[M+H]^+$; 94.64%.

Step 2. 2-((4-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide

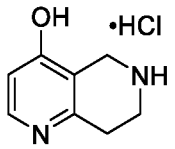


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide and 2.5 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride, except that 3 equivalents of DIPEA was used. The reaction was stirred at 70 °C in a pressure vial. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH). The fractions were concentrated under reduced pressure and lyophilized to obtain 2-((4-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid. Yield: 23.65%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.28 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.82 - 7.70 (m, 1H), 7.35 (dd, J = 3.1, 8.2 Hz, 1H), 7.29 (dt, J = 3.1, 8.6 Hz, 1H), 7.02 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.6 Hz, 1H), 6.41 - 6.04 (m, 1H), 4.73 (quin, J = 6.6 Hz, 1H), 4.31 - 4.05 (m, 4H), 3.90 - 3.68 (m, 3H), 3.65 (t, J = 6.8 Hz, 2H), 3.38 (s, 2H), 3.26 - 3.21 (m 2H), 2.88 (d, J = 7.9 Hz, 2H), 2.78 (br d, J = 5.1 Hz, 4H), 2.69 - 2.62 (m, 2H), 2.47 - 2.43 (m, 2H), 2.39 (br t, J = 7.1 Hz, 2H), 2.31 - 2.20 (m, 2H), 2.00 - 1.95 (m, 2H), 1.80 (quin, J = 6.9 Hz, 2H), 1.50 (quin, J = 7.1 Hz, 2H), 1.26 - 1.03 (m, 6H); LCMS (Method G): Rt = 1.88 min, m/z = 736.6 $[M+H]^+$; HPLC (Method A): Rt = 5.36 min, 99.84%.

Example 363. ***N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide** (Compound No. 385)

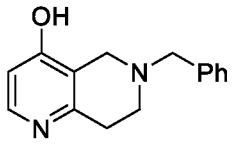


Step 1. 5,6,7,8-Tetrahydro-1,6-naphthyridin-4-ol hydrochloride



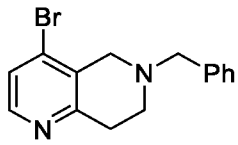
To a stirred solution of *tert*-butyl 4-hydroxy-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (25 g, 100 mmol) in TFE (250 mL), TMSCl (50.7 mL, 400 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred at RT for 1.5 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to afford crude 5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride (22.34 g, Quantitative yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.73 (br s, 1H), 9.89 (br s, 2H), 8.38 (d, J = 6.8 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 4.10 (br s, 2H), 3.49 - 3.39 (m, 2H), 3.25 - 3.17 (m, 2H); LCMS (Method G): Rt = 0.47 min, m/z = 151.1 $[M+H]^+$, 96.34%. This material was used without further purification.

Step 2. 6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



To a stirred solution of 5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride (22.34 g, 120 mmol) in DCM (250 mL), TEA (33.4 mL, 239 mmol) was added at RT. The reaction was stirred for 10 min. The reaction was concentrated under reduced pressure. The crude free amine was dissolved in MeOH (500 mL), and AcOH (1.369 mL, 23.94 mmol) and benzaldehyde (30.5 mL, 299 mmol) were added at RT. After 2 h, sodium triacetoxyborohydride (50.7 g, 239 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h and monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure and the residue was diluted with 10% MeOH in DCM (500 mL). The mixture was filtered through a Celite® pad, and the pad was washed with 10% MeOH in DCM (2 x 300 mL). The filtrate was concentrated under reduced pressure. The crude product was washed with MTBE (4 x 200 mL) and the solid was dried under vacuum to afford 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (25.12 g, 87% yield) as a solid. LCMS (Method G): Rt = 1.64 min, m/z = 481.3 $[M+H]^+$, 99.32%. This material was used without further purification.

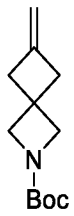
Step 3. 6-Benzyl-4-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine



In a 250 mL two neck round bottom flask under argon atmosphere, 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (5 g, 20.81 mmol) was dissolved in DMF (100 mL). To this solution, phosphorus oxybromide (8.95 g, 31.2 mmol) was added at 0 °C. The reaction was stirred at RT for 2 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with saturated sodium bicarbonate solution (50 mL) and the mixture was extracted with EtOAc (50 mL). The combined organic layer was washed

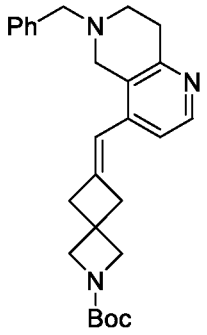
with brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (10% MeOH in DCM) to obtain 6-benzyl-4-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine (5.3 g, 79% yield) as a sticky liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 5.3 Hz, 1H), 7.50 (d, J = 5.1 Hz, 1H), 7.40 - 7.33 (m, 4H), 7.32 - 7.26 (m, 1H), 3.75 (s, 2H), 3.55 (s, 2H), 2.95 - 2.89 (m, 2H), 2.81 - 2.75 (m, 2H); LCMS (Method G): Rt = 1.99 min, m/z = 302.9 $[M+H]^+$, 94.36%.

Step 4. tert-Butyl 6-methylene-2-azaspiro[3.3]heptane-2-carboxylate



In a 500 mL two neck round bottom flask under an argon atmosphere, methyltriphenylphosphonium bromide (25.4 g, 71.0 mmol) was taken up in THF (100 mL), and potassium *tert*-butoxide (7.97 g, 71.0 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. To this reaction, *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (5.0 g, 23.67 mmol) in THF (15 mL) was added dropwise at 0 °C. The reaction was stirred at RT for 3 h, and reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction was diluted with water (100 mL) and the mixture was extracted with hexane (2 x 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 20% MeOH in DCM) to obtain *tert*-butyl 6-methylene-2-azaspiro[3.3]heptane-2-carboxylate (3.12 g, 62.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.78 (quin, J = 2.3 Hz, 2H), 3.85 (s, 4H), 2.83 (t, J = 2.4 Hz, 4H), 1.37 (s, 9H); LCMS (Method A): Rt = 2.58 min, m/z = 110.2 $[M-Boc+H]^+$, 99.77%.

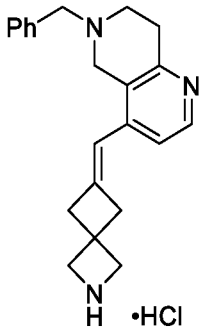
Step 5. tert-Butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptane-2-carboxylate



The reaction was performed following the same procedure in four batches (4 x 1 g).

In a 40 mL microwave vial, *tert*-butyl 6-methylene-2-azaspiro[3.3]heptane-2-carboxylate (1 g, 4.78 mmol), 6-benzyl-4-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine (1.159 g, 3.82 mmol), and K_2CO_3 (1.321 g, 9.56 mmol) were added in DMF (20 mL). The reaction was degassed with argon for 20 min. Palladium (II) acetate (0.107 g, 0.478 mmol) was added to this reaction mixture at RT, and the reaction was heated to 90 °C for 18 h. The reaction was monitored by TLC (100% EtOAc). The reaction mixtures from four batches were combined, water (25 mL) was added, and the mixture was extracted with EtOAc (50 mL). The mixture was filtered through a Celite® pad, and the pad was washed with EtOAc (2 x 50 mL). The filtrate was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted 5% MeOH in DCM) to obtain *tert*-butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptane-2-carboxylate (6.35 g, 76.31% combined yield) as a sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 5.0 Hz, 1H), 7.40 - 7.33 (m, 4H), 7.30 - 7.25 (m, 1H), 6.96 (d, J = 5.0 Hz, 1H), 6.11 (br s, 1H), 3.93 - 3.86 (m, 4H), 3.71 (s, 2H), 3.59 (s, 2H), 3.18 (br s, 2H), 3.05 (br s, 2H), 2.88 - 2.82 (m, 2H), 2.72 - 2.66 (m, 2H), 1.37 (s, 9H); LCMS (Method B): Rt = 1.51 min, m/z = 432.2 $[M+H]^+$, 99.12%.

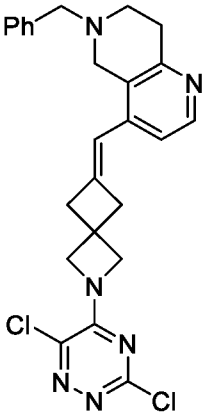
Step 6. 4-((2-Azaspiro[3.3]heptan-6-ylidene)methyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



The reaction was performed following the same procedure in two batches (2.4 g and 3.9 g).

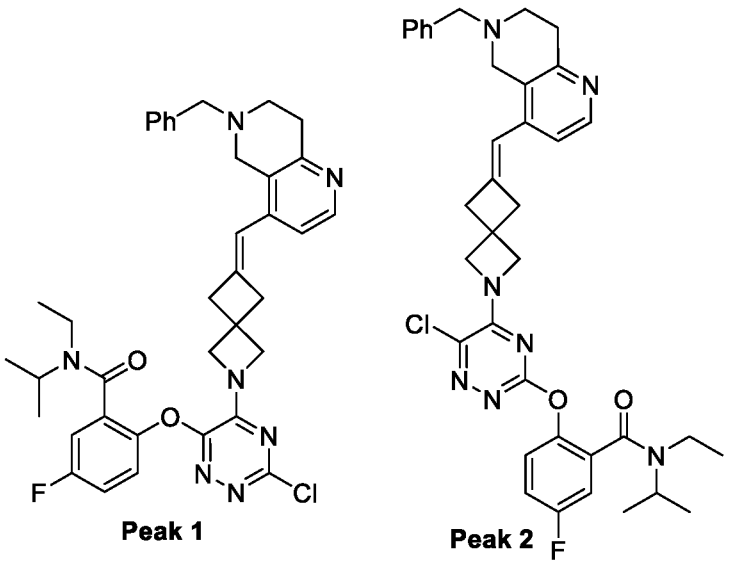
In a 50 mL two neck round bottom flask under argon atmosphere, *tert*-butyl 6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptane-2-carboxylate (2.4 g, 5.56 mmol) was dissolved in 2,2,2-triflouroethanol (30 mL). To this solution, TMSCl (2.132 mL, 16.68 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction mixtures from both batches were concentrated under reduced pressure and the residue was triturated with EtOAc (50 mL). The supernatant was decanted and the solid was dried under vacuum to obtain crude 4-((2-azaspiro[3.3]heptan-6-ylidene)methyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (6.1 g, 97.84% combined yield) as a solid. LCMS (Method G): Rt = 1.40 min, m/z = 332.1 $[M+H]^+$, 86.07%. This material was used without further purification.

Step 7. 6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-ylidene)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine



To a stirred solution of 4-((2-azaspiro[3.3]heptan-6-ylidene)methyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (6 g, 16.31 mmol) in DCM (100 mL), TEA (6.82 mL, 48.9 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred for 10 min at the same temperature. To this reaction mixture, 3,5,6-trichloro-1,2,4-triazine (3.01 g, 16.31 mmol) was added in one portion at 0 °C. The reaction was stirred at RT for 30 min, and the reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with water (50 mL) and the mixture was extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-ylidene)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (5.5 g, 50.9% yield). LCMS (Method B): Rt = 1.40 min, m/z = 479.4 $[M+H]^+$, 72.28%.

Step 8. 2-((5-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

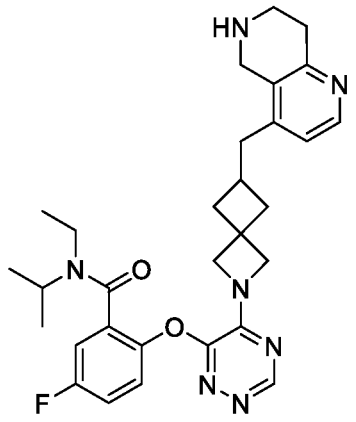


In a 50 mL two neck round bottom flask under a nitrogen atmosphere, 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-ylidene)methyl)-5,6,7,8-tetrahydro-1,6-

naphthyridine (5.5 g, 11.47 mmol) and *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (5.17 g, 22.94 mmol) were added in THF (110 mL). To this reaction mixture, DBU (5.14 mL, 34.4 mmol) was added at RT and the reaction was stirred at 40 °C for 18 h. The reaction was monitored by TLC (100% EtOAc). After completion, water (30 mL) was added to the reaction and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.97 g, 10.50% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, J = 5.0 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.40 - 7.32 (m, 6H), 7.31 - 7.24 (m, 1H), 6.98 (d, J = 5.1 Hz, 1H), 6.15 (br s, 1H), 4.71 - 4.60 (m, 2H), 4.33 - 4.20 (m, 2H), 3.74 - 3.56 (m, 4H), 3.30 - 3.27 (m, 2H), 3.18 - 3.11 (m, 2H), 3.10 - 2.98 (m, 1H), 2.86 (br t, J = 5.4 Hz, 2H), 2.73 - 2.66 (m, 2H), 1.16 - 0.73 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 2.27 min, m/z = 668.2 $[M+H]^+$, 83.14%.

Note: (5.2 g, LCMS-78% a mixture of regioisomers obtained).

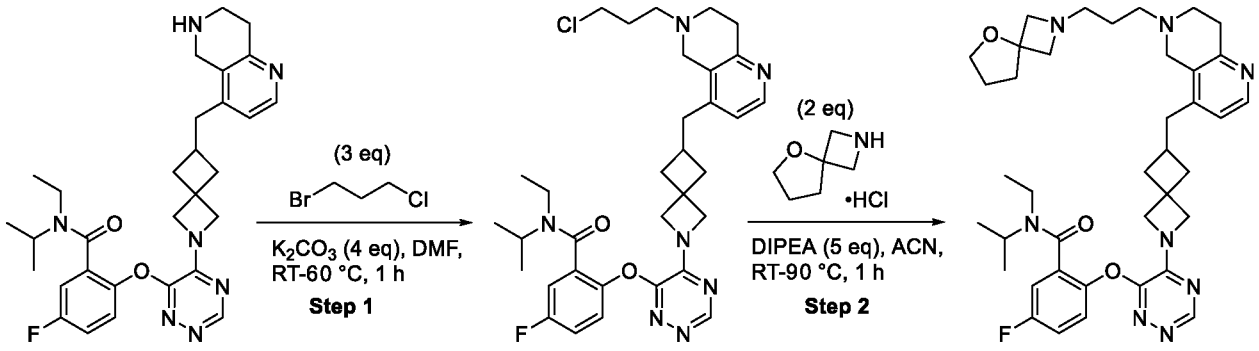
Step 9. N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



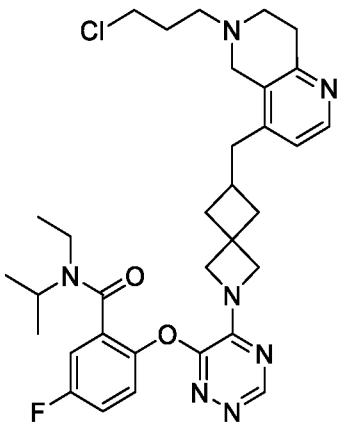
In a 50 mL round bottom flask under a nitrogen atmosphere, 2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methylene)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (970 mg, 1.452 mmol) was added in 2,2,2-triflouroethanol (20 mL). Pd/C (970 mg, 4.56 mmol) was added to this solution at

RT. The reaction was stirred at RT for 18 h under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the desired product (500 mg, 55.3% yield). HPLC (Method A): Rt = 4.41 min, 87.54%. A portion of this material (200 mg) was re-purified by Prep HPLC (Method AP) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (127 mg) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.21 (d, *J* = 5.0 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.39 - 7.30 (m, 2H), 6.94 (d, *J* = 5.0 Hz, 1H), 4.60 - 4.39 (m, 2H), 4.32 - 4.03 (m, 2H), 3.82 (s, 2H), 3.60 (spt, *J* = 6.5 Hz, 1H), 3.47 - 3.37 (m, 1H), 3.14 - 3.01 (m, 1H), 2.98 (t, *J* = 5.9 Hz, 2H), 2.75 (br t, *J* = 5.8 Hz, 2H), 2.61 - 2.54 (m, 2H), 2.47 - 2.28 (m, 2H), 2.02 - 1.89 (m, 2H), 1.14 - 0.65 (m, 9H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.59 min, m/z = 546.3 $[M+H]^+$; HPLC (Method G): Rt = 4.42 min, 99.30%.

Example 364. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 386)

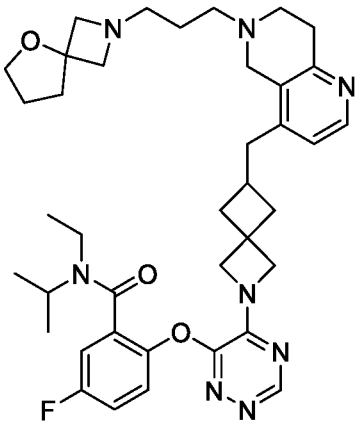


Step 1. 2-((5-(6-((6-(3-Chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalents of 1-bromo-3-chloropropane, except that 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was used, to afford crude 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a sticky liquid. This material was used without further purification. Yield: 71.2%; LCMS (Method G): Rt = 1.98 min, m/z = 622.4 $[M+H]^+$, 77.34%.

Step 2. 2-((5-(6-((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

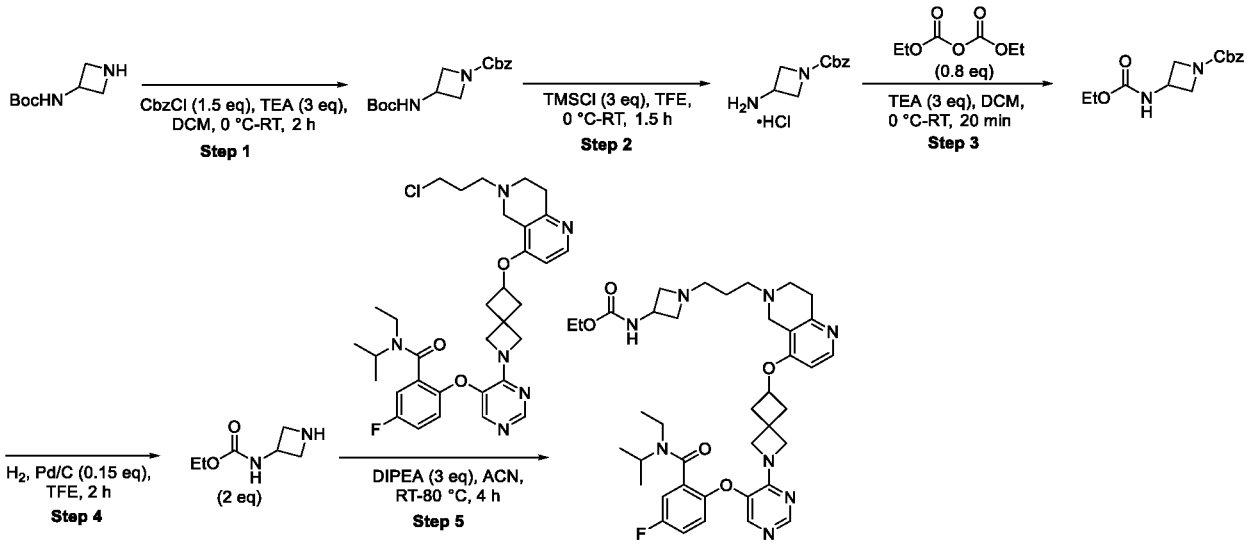


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 1 equivalent of 2-((5-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-

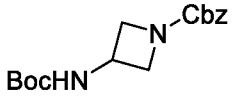
N-ethyl-5-fluoro-*N*-isopropylbenzamide and 2 equivalents of 5-oxa-2-azaspiro[3.4]octane hydrochloride. The reaction was stirred at 90 °C in a pressure vial. After completion, the crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by Prep HPLC (Method B). The product fractions were concentrated under reduced pressure and lyophilized to afford 2-((5-(6-((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)methyl)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 14.87%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.22 (d, J = 5.0 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.95 (d, J = 4.9 Hz, 1H), 4.65 - 4.42 (m, 2H), 4.34 - 3.98 (m, 2H), 3.68 - 3.57 (m, 3H), 3.50 (s, 2H), 3.46 - 3.37 (m, 1H), 3.28 - 3.22 (m, 2H), 3.18 - 2.98 (m, 1H), 2.92 - 2.81 (m, 4H), 2.68 (br t, J = 5.3 Hz, 2H), 2.61 (br d, J = 7.0 Hz, 2H), 2.41 (br t, J = 7.0 Hz, 2H), 2.37 - 2.28 (m, 2H), 2.01 - 1.92 (m, 4H), 1.79 (quin, J = 6.9 Hz, 2H), 1.53 (quin, J = 7.0 Hz, 2H), 1.26 - 0.66 (m, 9H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.77 min, m/z = 699.4 $[M+H]^+$; HPLC (Method G): Rt = 4.95 min, 98.68%.

Example 365. Ethyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate (Compound No. 197)

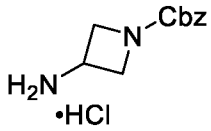


Step 1. Benzyl 3-((tert-butoxycarbonyl)amino)azetidine-1-carboxylate



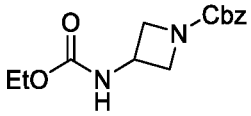
In a dried, 25 mL round bottom flask under a nitrogen atmosphere, *tert*-butyl azetidin-3-ylcarbamate (600 mg, 3.48 mmol) was added in DCM (2 mL). TEA (1.06 mg, 10.45 mmol) and CbzCl (891 mg, 5.23 mmol) were added to this solution at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with water (20 mL) and the mixture was extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 3% MeOH in DCM) to obtain benzyl 3-((*tert*-butoxycarbonyl)amino)azetidine-1-carboxylate (720 mg, 61.0% yield) as a gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54 (br d, J = 7.1 Hz, 1H), 7.44 - 7.26 (m, 5H), 5.03 (s, 2H), 4.35 - 4.22 (m, 1H), 4.21 - 4.05 (m, 2H), 3.88 - 3.65 (m, 2H), 1.38 (s, 9H); LCMS (Method B): Rt = 2.00 min, m/z = 251.1 $[M+H-56]^+$, 90.49%.

Step 2. Benzyl 3-aminoazetidine-1-carboxylate hydrochloride



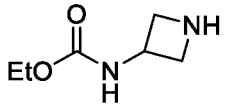
In a dried, 50 mL round bottom flask under a nitrogen atmosphere, benzyl 3-((*tert*-butoxycarbonyl)amino)azetidine-1-carboxylate (700 mg, 2.285 mmol) was dissolved in TFE (15 mL). To this solution, TMSCl (0.876 mL, 6.85 mmol) was added at 0 °C, and the reaction was stirred at RT for 1.5 h. The reaction progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure to obtain crude benzyl 3-aminoazetidine-1-carboxylate hydrochloride (555 mg, 79% yield) as a solid. This material was used without further purification. LCMS (Method B): Rt = 1.05 min, m/z = 207.2 $[M+H]^+$, 92.83%.

Step 3. Benzyl 3-((ethoxycarbonyl)amino)azetidine-1-carboxylate



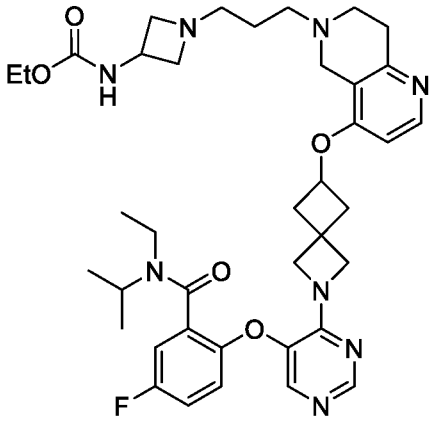
In a 4 mL pressure vial under a nitrogen atmosphere, benzyl 3-aminoazetidine-1-carboxylate hydrochloride (400 mg, 1.648 mmol) was added in DCM (1 mL). To this solution, TEA (0.689 mL, 4.94 mmol) and diethyl dicarbonate (143 mg, 1.318 mmol) were added at 0 °C, and the reaction was stirred at RT for 20 min. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 3% MeOH in DCM) to obtain benzyl 3-((ethoxycarbonyl)amino)azetidine-1-carboxylate (180 mg, 38.3% yield) as a gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (br d, J = 7.1 Hz, 1H), 7.43 - 7.26 (m, 5H), 5.04 (s, 2H), 4.40 - 4.25 (m, 1H), 4.22 - 4.08 (m, 2H), 3.99 (q, J = 7.1 Hz, 2H), 3.92 - 3.74 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H); LCMS-ELSD (Method B): Rt = 1.87 min, m/z = 279.2 $[M+H]^+$, 97.55%.

Step 4. Ethyl azetidin-3-ylcarbamate



To a stirred solution of benzyl 3-((ethoxycarbonyl)amino)azetidine-1-carboxylate (140 mg, 0.503 mmol) in TFE (5 mL), Pd-C (80 mg, 0.075 mmol) was added at RT. The reaction was stirred at RT for 2 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (3 x 10 mL). The filtrate was concentrated under reduced pressure to obtain crude ethyl azetidin-3-ylcarbamate (70 mg, 97% yield) as a liquid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (br s, 1H), 4.28 (br s, 1H), 3.97 (q, J = 7.0 Hz, 2H), 3.61 - 3.40 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H), one proton merged with solvent peaks.

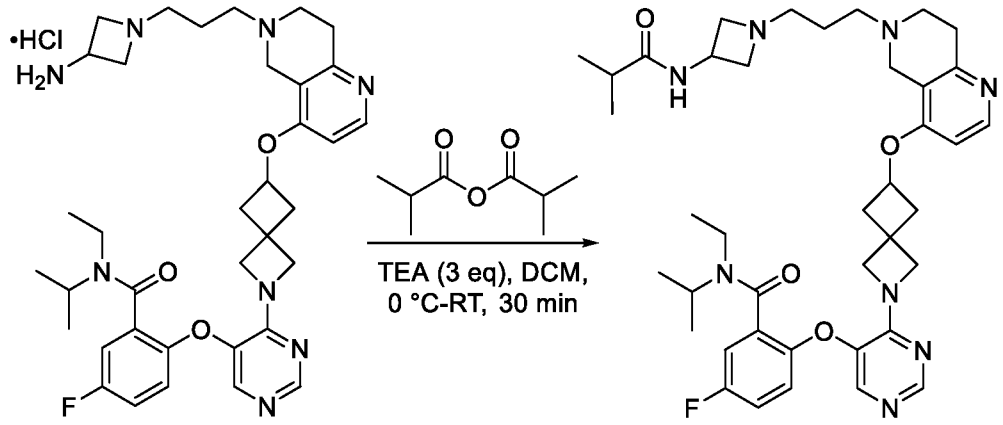
Step 5. Ethyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate



This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2-((4-(6-((6-(3-chloropropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of ethyl azetidin-3-ylcarbamate and 3 equivalents of DIPEA were used. The reaction was stirred at 80 °C. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain ethyl (1-(3-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)propyl)azetidin-3-yl)carbamate as a solid.

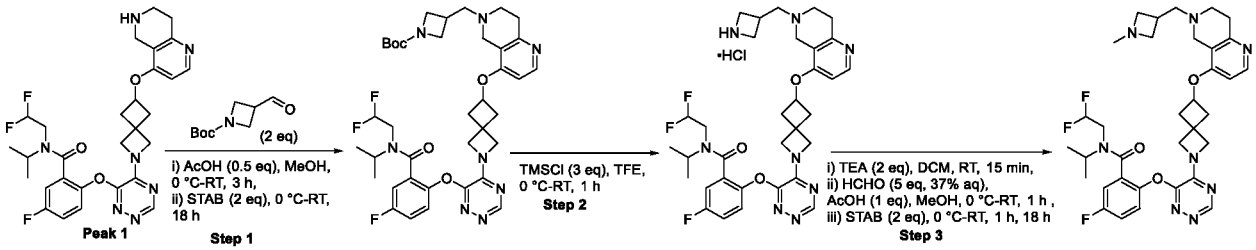
Yield: 42.5%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.53 (br d, J = 7.5 Hz, 1H), 7.35 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.61 (m, 1H), 4.81 - 4.66 (m, 1H), 4.32 - 3.92 (m, 7H), 3.82 - 3.71 (m, 1H), 3.46 (br t, J = 7.1 Hz, 2H), 3.43 - 3.40 (m, 1H), 3.29 - 3.11 (m, 1H), 2.85 - 2.61 (m, 9H), 2.47 - 2.42 (m, 2H), 2.41 - 2.31 (m, 3H), 2.31 - 2.21 (m, 2H), 1.48 (quin, J = 7.1 Hz, 2H), 1.26 - 0.95 (m, 12H); LCMS (Method D): Rt = 1.77 min, m/z = $[M+H]^+$, 731.4; HPLC (Method A): Rt = 5.01 min, 97.22%.

Example 366. ***N*-Ethyl-5-fluoro-2-((4-(6-((6-(3-(3-isobutyramidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide** (Compound No. 185)

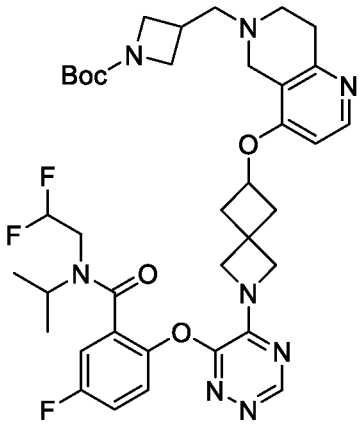


This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 1 equivalent of 2-((4-(6-((6-(3-(3-aminoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 1 equivalent of isobutyric anhydride, except that 3 equivalents of Et_3N was used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-ethyl-5-fluoro-2-((4-(6-((6-(3-(3-isobutyramidoazetidin-1-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid. Yield: 49.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 8.10 (br d, J = 7.4 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.70 - 6.63 (m, 1H), 4.84 - 4.64 (m, 1H), 4.34 - 4.03 (m, 5H), 3.75 (spt, J = 6.5 Hz, 1H), 3.46 (t, J = 7.2 Hz, 2H), 3.43 - 3.36 (m, 3H), 3.29 - 3.09 (m, 1H), 2.85 - 2.70 (m, 6H), 2.70 - 2.62 (m, 2H), 2.48 - 2.44 (m, 1H), 2.42 - 2.21 (m, 6H), 1.49 (quin, J = 7.0 Hz, 2H), 1.25 - 1.01 (m, 9H), 0.97 (d, J = 6.9 Hz, 6H); LCMS (Method D): Rt = 1.69 min, m/z = 729.4 $[M+H]^+$; HPLC (Method A): Rt = 5.26 min, 99.37%.

Example 367. ***N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide** (Compound No. 387)



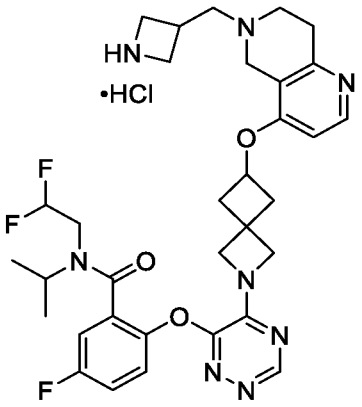
Step 1. tert-Butyl 3-((4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 2 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, except that 1 equivalents of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, 2 equivalents of STAB and 0.5 equivalent of AcOH were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 6% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate as a solid.

Yield: 70.1%; LCMS (Method F): Rt = 2.09 min, m/z = 753.3 $[M+H]^+$, 99.53%.

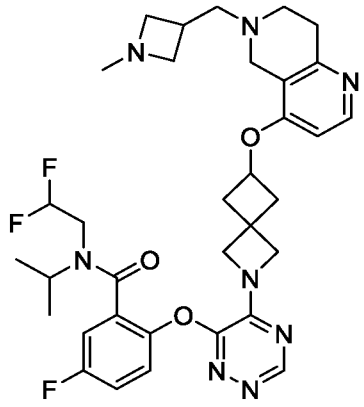
Step 2. 2-((5-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(6-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate. The crude was triturated with EtOAc, and the supernatant was decanted. The solid was dried under vacuum to afford crude 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide hydrochloride as a solid. This material was used without further purification.

Yield: 92%; LCMS (Method G): Rt = 2.04 min, m/z = 653.3 $[M+H]^+$, 90.66%.

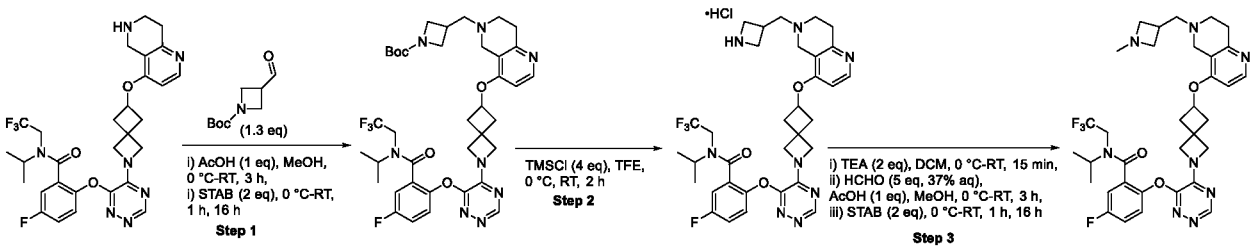
Step 3. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



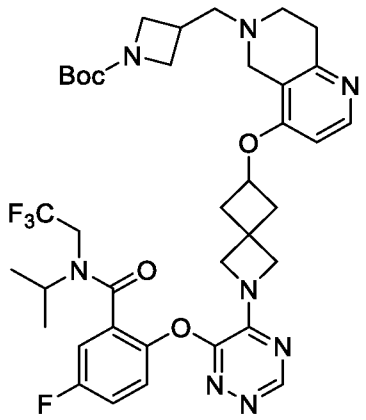
This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide hydrochloride and 5 equivalents of formaldehyde (37% in H_2O), except that 2 equivalents of STAB was used. The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 30.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.51 - 7.37 (m, 3H), 6.68 (d, J = 5.6 Hz, 1H), 6.37 - 5.98 (m, 1H), 4.86 - 4.72 (m, 1H), 4.65 - 4.41 (m, 2H), 4.29 - 4.10 (m, 2H), 3.82 - 3.66 (m, 2H), 3.63 - 3.50 (m, 1H), 3.38 (s, 2H), 2.87 - 2.70 (m, 7H), 2.68 - 2.62 (m, 5H), 2.36 - 2.28 (m, 2H), 2.17 (s, 3H), 1.19 - 0.65 (m, 6H), one proton merged with solvent peaks; LCMS (Method B): Rt = 1.05 min, m/z = 667.2 $[M+H]^+$; HPLC (Method A): Rt = 4.67 min, 99.09%.

Example 368. 5-Fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 315)



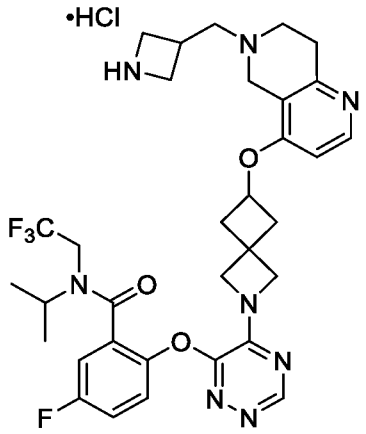
Step 1. tert-Butyl 3-((4-((2-(6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1.3 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, except that 1 equivalent of 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide, 2 equivalents of STAB and 1 equivalent of AcOH were used. The reaction was diluted with water and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was washed with brine solution and dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate as a solid.

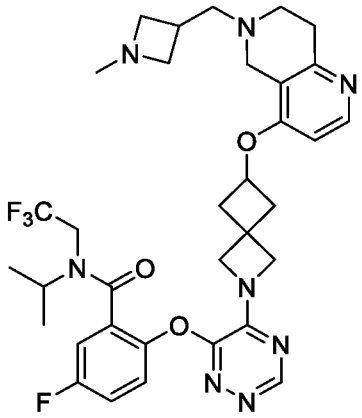
Yield: 66.2%; LCMS (Method G): Rt = 2.07 min, m/z = 771.7 $[M+H]^+$, 99.28%.

Step 2. 2-((5-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with 1 equivalent of *tert*-butyl 3-((4-((2-(6-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure. The crude product was triturated with EtOAc, and the organic layer was decanted. The solid was dried under vacuum to obtain crude 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride as a solid.
Yield: 80%; LCMS (Method G): Rt = 1.80 min, m/z = 671.6 $[M+H]^+$, 88.41%. This material was used without further purification.

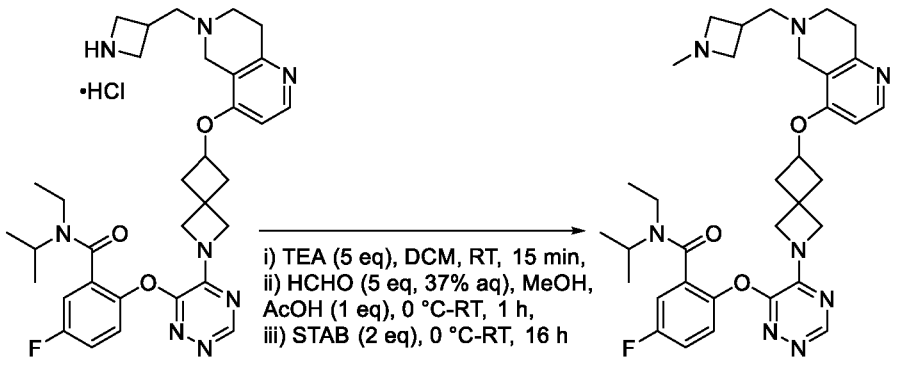
Step 3. 5-Fluoro-N-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride and 5 equivalents of formaldehyde (37% in H_2O), except that 2 equivalents of STAB was used. The reaction was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain 5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide as a solid.

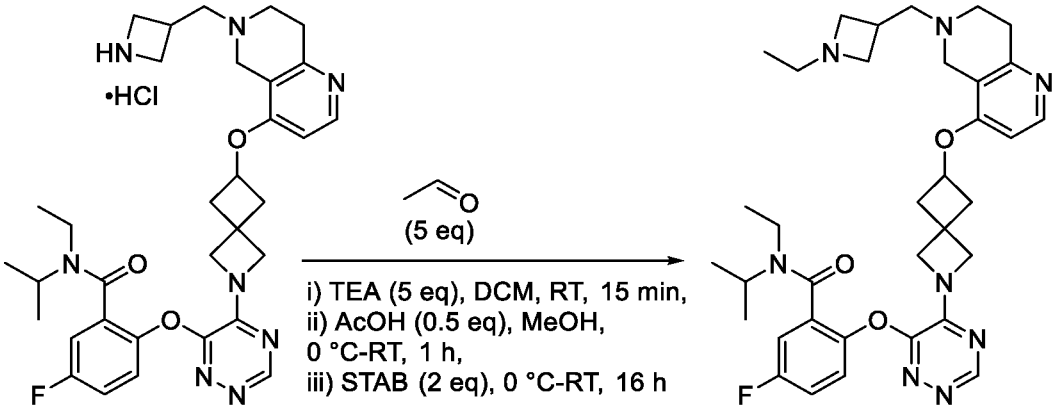
Yield: 40.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.52 - 7.39 (m, 3H), 6.67 (br d, J = 5.4 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.64 - 4.45 (m, 2H), 4.34 - 3.98 (m, 4H), 3.83 - 3.72 (m, 1H), 3.38 (s, 2H), 2.85 - 2.70 (m, 6H), 2.68 - 2.61 (m, 5H), 2.38 - 2.24 (m, 2H), 2.17 (br s, 3H), 1.45 - 0.68 (m, 6H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.76 min, m/z = 685.7 $[M+H]^+$; HPLC (Method A): Rt = 4.47 min, 99.82%.

Example 369. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 337)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 5 equivalents of formaldehyde (37% in H_2O), except that 5 equivalents of TEA and 2 equivalents of STAB were used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid. Yield: 43.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (br d, J = 5.0 Hz, 1H), 7.50 - 7.31 (m, 3H), 6.68 (br d, J = 4.9 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.67 - 4.49 (m, 2H), 4.30 - 4.11 (m, 2H), 3.62 (br s, 1H), 3.38 (br s, 2H), 3.16 - 2.94 (m, 2H), 2.89 - 2.71 (m, 7H), 2.65 (br s, 2H), 2.33 (br s, 2H), 2.18 (br s, 3H), 1.19 - 0.64 (m, 9H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.57 min, m/z = 631.6 $[M+H]^+$; HPLC (Method A): Rt = 4.43 min, 98.41%.

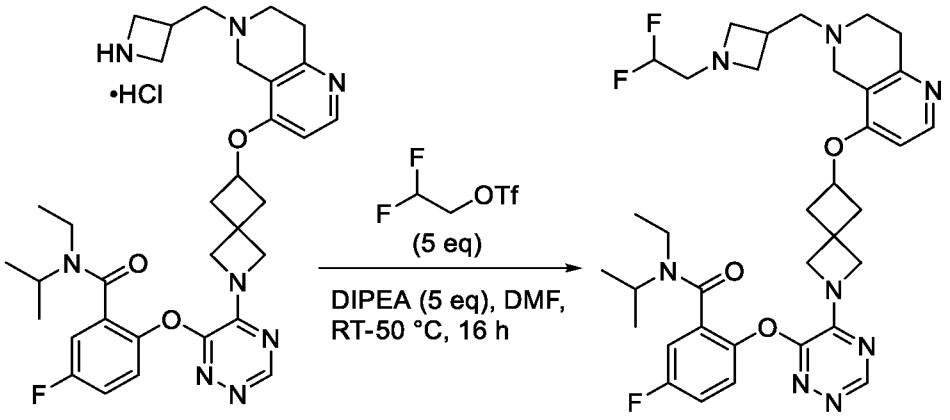
Example 370. *N*-Ethyl-2-((5-(6-((6-((1-ethylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 388)



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 5 equivalents of acetaldehyde, except that 5 equivalents of TEA, 0.5 equivalent of AcOH and 2 equivalents of STAB were used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method V). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-ethyl-2-((5-(6-((6-((1-ethylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid.

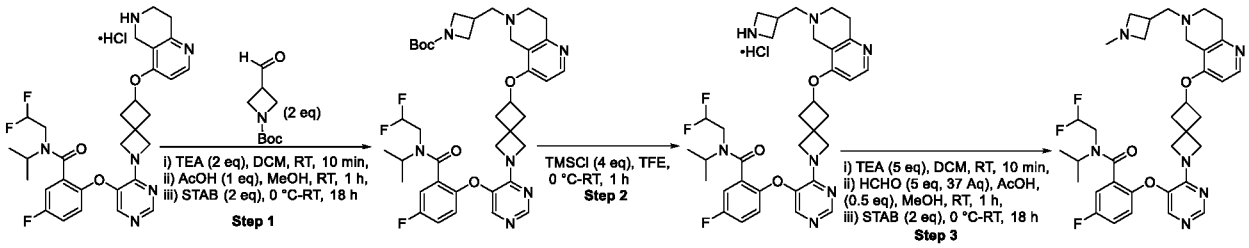
Yield: 18.94%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.49 - 7.31 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 4.78 (quin, J = 6.5 Hz, 1H), 4.68 - 4.47 (m, 2H), 4.33 - 4.11 (m, 2H), 3.67 - 3.56 (m, 1H), 3.39 (s, 2H), 3.15 - 2.97 (m, 2H), 2.89 - 2.74 (m, 6H), 2.75 - 2.61 (m, 6H), 2.39 - 2.25 (m, 2H), 1.17 - 0.67 (m, 12H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.59 min, m/z = 645.3 $[M+H]^+$; HPLC (Method G): Rt = 4.41 min, 96.71%.

Example 371. 2-((5-(6-((6-((1-(2,2-Difluoroethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 389)

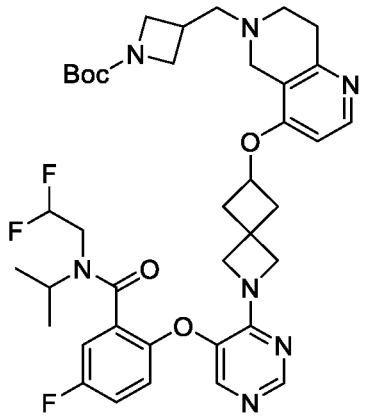


To a stirred solution of 2-((5-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.3 g, 0.459 mmol) and 2,2-difluoroethyl trifluoromethanesulfonate (0.492 g, 2.296 mmol) in DMF (3 ml), DIPEA (0.297 g, 2.296 mmol) was added. The reaction was stirred at 50 °C for 16 h. The reaction was monitored by TLC (20% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method H). The pure fractions were concentrated under reduced pressure and lyophilized to obtain 2-((5-(6-((6-((1-(2,2-difluoroethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.012 g, 3.79% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.49 - 7.32 (m, 3H), 6.68 (d, J = 5.7 Hz, 1H), 6.11 - 5.72 (m, 1H), 4.78 (quin, J = 6.5 Hz, 1H), 4.67 - 4.47 (m, 2H), 4.33 - 4.10 (m, 2H), 3.69 - 3.55 (m, 1H), 3.48 - 3.37 (m, 5H), 3.17 - 3.00 (m, 1H), 2.93 (br s, 2H), 2.85 - 2.75 (m, 5H), 2.74 - 2.62 (m, 5H), 2.37 - 2.24 (m, 2H), 1.18 - 0.65 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.62 min, m/z = 681.2 $[M+H]^+$; HPLC (Method G): Rt = 5.08 min, 98.88%.

Example 372. *N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 341)



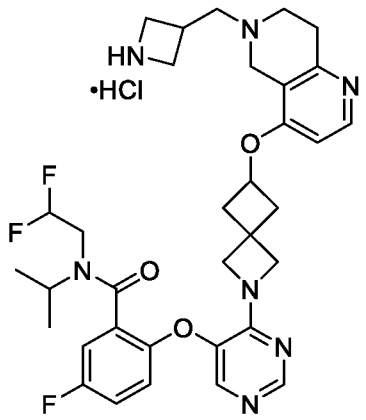
Step 1. tert-Butyl 3-((4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 2 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, except that 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 2 equivalents of STAB were used. After completion, the reaction was concentrated under reduced pressure. The crude was diluted with 10% $NaHCO_3$ solution and the mixture was extracted with DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to obtain *tert*-butyl 3-((4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate.

Yield: 65.0%; LCMS (Method G): Rt = 2.47 min, m/z = 752.8 $[M+H]^+$, 98.66%.

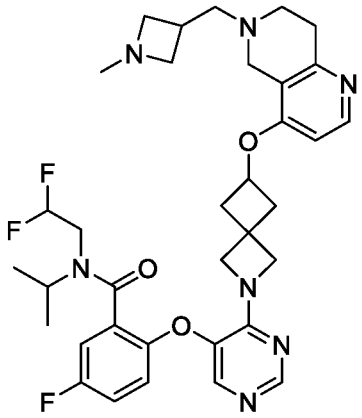
Step 2. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with 1 equivalent of *tert*-butyl 3-((4-((2-(5-(2-((2,2-difluoroethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure, the residue was triturated with EtOAc, and the supernatant was decanted. The solid was dried under vacuum to obtain 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide hydrochloride as a solid. This material was used without further purification.

Yield: 95%; LCMS (Method G): Rt = 1.60 min, m/z = 652.6 $[M+H]^+$, 99.05%.

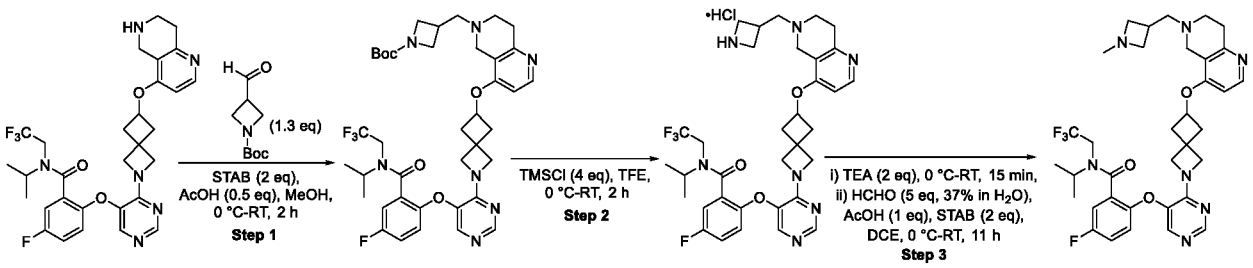
Step 3. N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



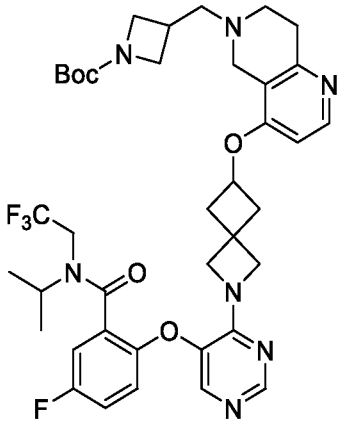
This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide hydrochloride and 5 equivalents of formaldehyde (37% in H_2O), except that 0.5 equivalent of AcOH, 5 equivalents of TEA and 2 equivalents of STAB were used. After work-up, the crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under pressure and lyophilized to afford *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 42.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.84 - 7.67 (m, 1H), 7.36 (dd, J = 3.0, 8.1 Hz, 1H), 7.29 (dt, J = 3.0, 8.6 Hz, 1H), 7.02 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.8 Hz, 1H), 6.41 - 6.05 (m, 1H), 4.73 (quin, J = 6.4 Hz, 1H), 4.28 - 4.04 (m, 4H), 3.92 - 3.81 (m, 1H), 3.80 - 3.64 (m, 2H), 3.37 (s, 2H), 2.81 - 2.71 (m, 6H), 2.68 - 2.55 (m, 6H), 2.30 - 2.20 (m, 2H), 2.17 (s, 3H), 1.27 - 1.02 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.73 min, m/z = 666.6 $[M+H]^+$; HPLC (Method A): Rt = 5.02 min, 99.10%.

Example 373. 5-Fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 390)



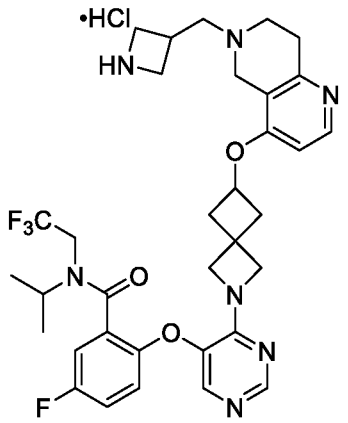
Step 1. tert-Butyl 3-((4-((2-(5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 26, step 1, starting with 1.3 equivalents of *tert*-butyl 3-formylazetidine-1-carboxylate, except that 1 equivalent of 5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide, 2 equivalents of STAB and 0.5 equivalent of AcOH were used. After completion, water was added to the reaction, and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to afford *tert*-butyl 3-((4-((2-(5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate as a solid. Yield: 35.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.81 (s, 1H), 7.37 - 7.27 (m, 2H), 7.02 (dd, J = 4.4, 8.9 Hz, 1H), 6.65 (d, J = 5.8 Hz, 1H), 4.73

(quin, *J* = 6.5 Hz, 1H), 4.39 - 4.03 (m, 6H), 4.00 - 3.85 (m, 3H), 3.57 - 3.46 (m, 2H), 3.42 (br s, 2H), 2.90 - 2.64 (m, 9H), 2.28 - 2.16 (m, 2H), 1.37 (s, 9H), 1.18 - 1.04 (m, 6H); LCMS (Method G): Rt = 2.07 min, m/z = 770.2 $[M+H]^+$, 95.83%.

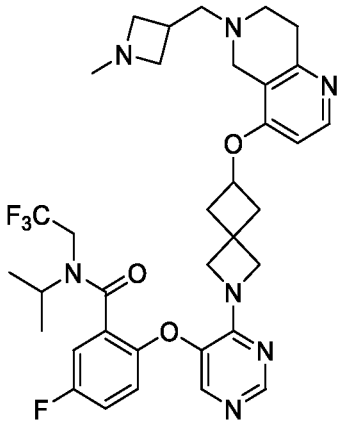
Step 2. 2-((4-(6-((6-(Azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 26, step 2, starting with *tert*-butyl 3-((4-((2-(5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methyl)azetidine-1-carboxylate, except that 4 equivalents of TMSCl was used. After completion, the crude was concentrated under reduced pressure. The residue was triturated with EtOAc, and the supernatant was decanted. The solid was dried under reduced pressure to obtain crude 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride. This material was used without further purification.

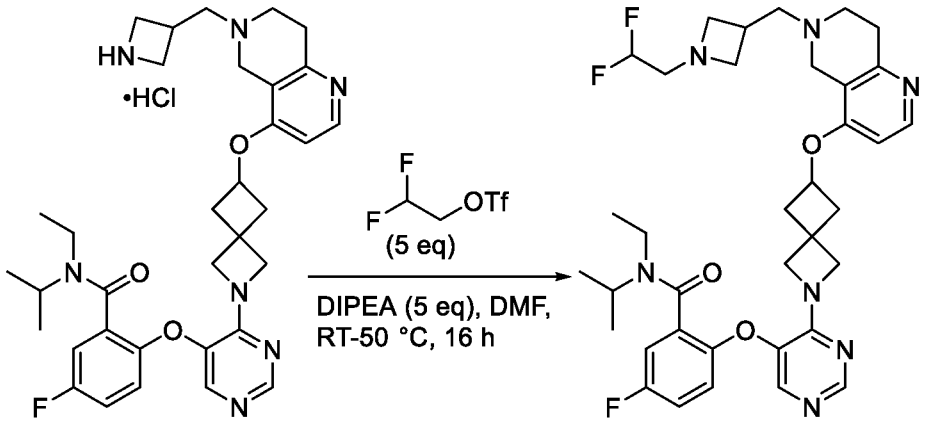
Yield: 78%; LCMS (Method G): Rt = 2.23 min, m/z = 670.3 $[M+H]^+$, 61.70%.

Step 3. 5-Fluoro-N-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



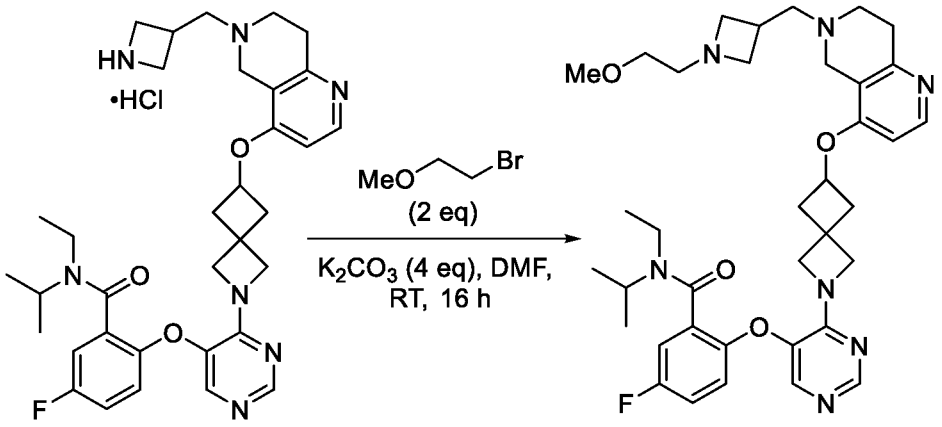
This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide hydrochloride, except that 5 equivalents of HCHO (37% in H_2O) and 2 equivalents of STAB were used, and DCE was used as the solvent. After completion, the reaction was diluted with 10% $NaHCO_3$ solution and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the resulting crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-methylazetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide as a solid. Yield: 30.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.38 - 7.22 (m, 2H), 7.03 (dd, J = 4.3, 8.9 Hz, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.72 (quin, J = 6.3 Hz, 1H), 4.38 - 4.04 (m, 6H), 4.01 - 3.86 (m, 1H), 3.37 (s, 2H), 3.31 - 3.28 (m, 2H), 2.82 - 2.71 (m, 6H), 2.70 - 2.56 (m, 5H), 2.28 - 2.19 (m, 2H), 2.17 (s, 3H), 1.35 – 0.9 (m, 6H); LCMS (Method B): Rt = 1.05 min, m/z = 684.2 $[M+H]^+$; HPLC (Method A): Rt = 5.08 min, 97.96%.

Example 374. 2-((4-(6-((6-((1-(2,2-Difluoroethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 391)



This compound was synthesized following the procedure described for the synthesis of Example 371, starting with 5 equivalents 2,2-difluoroethyl trifluoromethanesulfonate, except that 1 equivalent of 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride was used. After completion, the reaction was diluted with cold water and the mixture was extracted with EtOAc. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method Y). The product fractions were concentrated under reduced pressure and lyophilized to afford 2-((4-(6-((6-((1-(2,2-difluoroethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (15.79 mg, 4.98% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 - 8.15 (m, 1H), 7.78 - 7.62 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 - 6.61 (m, 1H), 6.08 - 5.74 (m, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.04 (m, 4H), 3.84 - 3.67 (m, 1H), 3.48 - 3.42 (m, 3H), 3.41 - 3.35 (m, 3H), 3.27 - 3.11 (m, 2H), 2.97 - 2.90 (m, 2H), 2.83 - 2.72 (m, 5H), 2.70 - 2.65 (m, 4H), 2.29 - 2.19 (m, 2H), 1.24 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.79 min, m/z = 680.2 $[M+H]^+$; HPLC (Method G): Rt = 5.27 min, 99.92%.

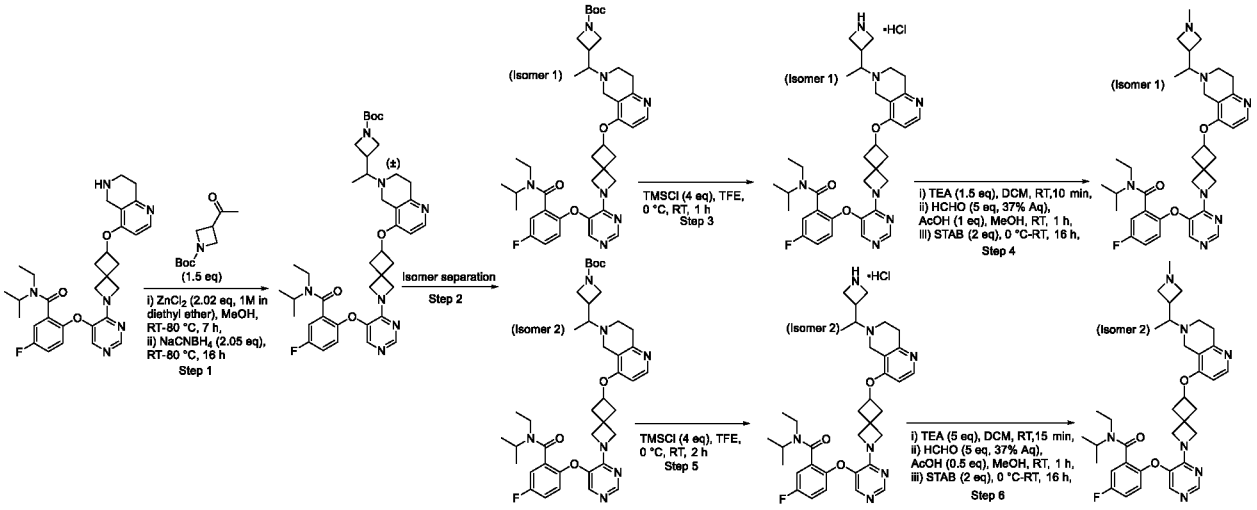
Example 375. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-(2-methoxyethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 392)



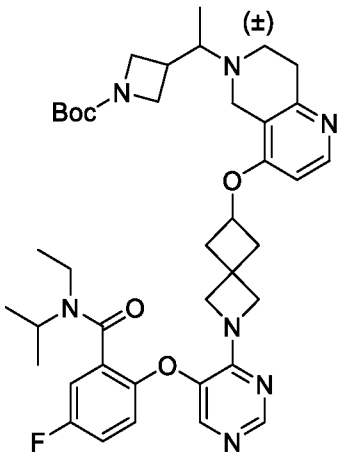
To a stirred solution of 2-((4-(6-((6-(azetidin-3-ylmethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.325 g, 0.498 mmol) in DMF (4 mL), K_2CO_3 (0.275 g, 1.993 mmol) was added at RT. To this reaction mixture 1-bromo-2-methoxyethane (0.139 g, 0.997 mmol) was added, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was quenched with ice-cold water (20 mL) and extracted with 10% MeOH in DCM (3 x 25 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then Prep HPLC (Method C) to obtain *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-((1-(2-methoxyethyl)azetidin-3-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (11 mg, 3.24% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 - 8.41 (m, 1H), 8.24 (d, *J* = 5.6 Hz, 1H), 7.84 - 7.82 (m, 1H), 7.09 - 7.00 (m, 2H), 6.77 - 6.68 (m, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 4.70 - 4.59 (m, 1H), 4.40 - 4.25 (m, 2H), 4.24 - 4.16 (m, 2H), 3.94 - 3.81 (m, 1H), 3.63 - 3.57 (m, 2H), 3.56 - 3.50 (m, 1H), 3.49 (br s, 2H), 3.42 - 3.37 (m, 3H), 3.36 (s, 3H), 3.01 - 2.84 (m, 5H), 2.83 - 2.70 (m, 6H), 2.67 (t, *J* = 5.4 Hz, 2H), 2.42 - 2.33 (m, 2H), 1.34 - 1.26 (m, 4H), 1.20 - 1.16 (m, 5H); LCMS (Method G): Rt = 1.67 min, m/z = 674.4 $[M+H]^+$; HPLC (Method G): Rt = 4.75 min, 99.05%.

Example 376. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 393)

Example 377. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 394)



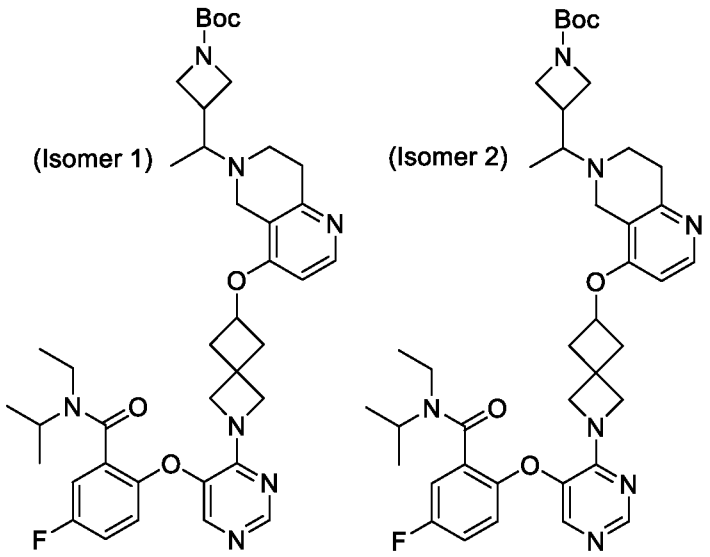
Step 1. (±)-tert-Butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate



In an 8 mL pressure vial under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.66 g, 1.207 mmol) was dissolved in MeOH (16 mL). To this solution, *tert*-butyl 3-acetylazetidine-1-carboxylate (0.361 g, 1.811 mmol) and zinc chloride (2.439 mL, 2.439 mmol) were added at RT. The reaction was stirred at 80 °C. After 7 h, sodium

cyanoborohydride (0.156 g, 2.475 mmol) was added to the reaction mixture at RT. The reaction was stirred at 80 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to afford (±)-*tert*-butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (600 mg, 60.3% yield) as a solid. LCMS (Method G): Rt = 2.43 min, m/z = 730.4 $[M+H]^+$; HPLC (Method A): Rt = 6.49 min, 95.82%; Chiral SFC (Method AAA): Peak 1: Rt = 6.6 min, 49.67%; Peak 2: Rt = 12.21 min, 48.27%.

Step 2. (E1)-tert-Butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate and (E2)-tert-butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate



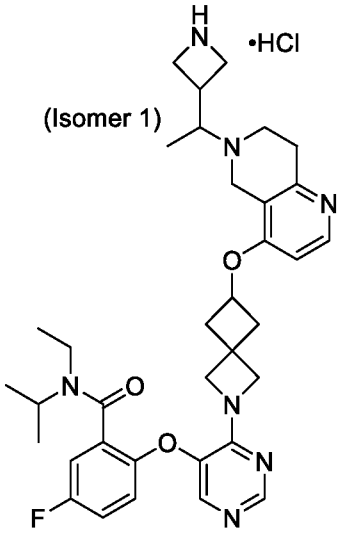
(±)-*tert*-Butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (500 mg) was purified by chiral Prep SFC (Method S) to obtain both isomers, (*E1*)-*tert*-butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-

yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (190 mg, 36.1% yield) and (*E2*)-*tert*-butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (170 mg, 33.8% yield).

Isomer 1. LCMS (Method G): Rt = 2.11 min, m/z = 730.2 $[M+H]^+$; HPLC (Method A): Rt = 6.47 min, 98.25%; Chiral SFC (Method AAA): Rt = 6.35 min, 100%.

Isomer 2. LCMS (Method G): Rt = 2.10 min, m/z = 730.2 $[M+H]^+$; HPLC (Method A): Rt = 6.46 min, 99.25%; Chiral SFC (Method AAA): Rt = 11.89 min, 100%.

Step 3. (E1)-2-((4-(6-((6-(1-(Azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride

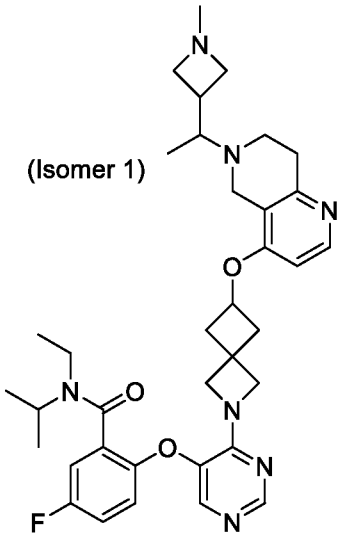


In a 50 mL round bottom flask, (*E1*)-*tert*-butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (190 mg, 0.260 mmol) was added in TFE (2 mL). TMSCl (0.133 mL, 1.041 mmol) was added to this solution at 0 °C. The reaction was stirred to RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to afford crude *(E1)*-2-((4-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (160 mg, 85% yield) as a solid. This material was used without further purification.

LCMS (Method G): Rt = 1.61 min, m/z = 630.2 $[M+H]^+$, 91.67%.

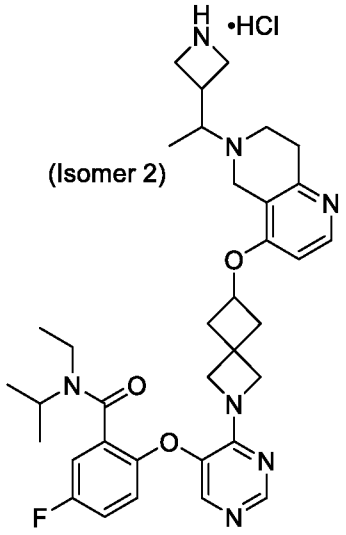
Step 4. (E1)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



In a 50 mL round bottom flask under a nitrogen atmosphere, *(E1)*-2-((4-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (160 mg, 0.240 mmol) and triethylamine (0.050 mL, 0.360 mmol) were added in DCM (4 mL). The reaction was stirred for 10 min and concentrated under reduced pressure. The residue was taken up in MeOH (2 mL), and formaldehyde (0.120 mL, 1.201 mmol, 37% in H_2O) and AcOH (0.014 mL, 0.240 mmol) were added at RT. The reaction was stirred at RT for 1 h, and then sodium triacetoxyborohydride (102 mg, 0.480 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain *(E1)*-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-

1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (74.57 mg, 47.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 - 8.14 (m, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.68 - 6.61 (m, 1H), 4.79 - 4.68 (m, 1H), 4.47 - 4.08 (m, 4H), 3.82 - 3.70 (m, 1H), 3.47 (s, 2H), 3.44 - 3.37 (m, 1H), 3.29 - 3.12 (m, 2H), 2.94 - 2.83 (m, 1H), 2.82 - 2.71 (m, 6H), 2.67 - 2.63 (m, 1H), 2.61 - 2.55 (m, 1H), 2.30 - 2.21 (m, 2H), 2.16 (s, 3H), 1.25 - 0.97 (m, 9H), 0.88 (d, J = 6.5 Hz, 3H), two protons merged with solvent peaks; LCMS (Method G): Rt = 1.66 min, m/z = 644.2 $[M+H]^+$; HPLC (Method A): Rt = 4.77 min, 99.31%; Chiral SFC (Method B): Rt = 1.26 min, 99.66%.

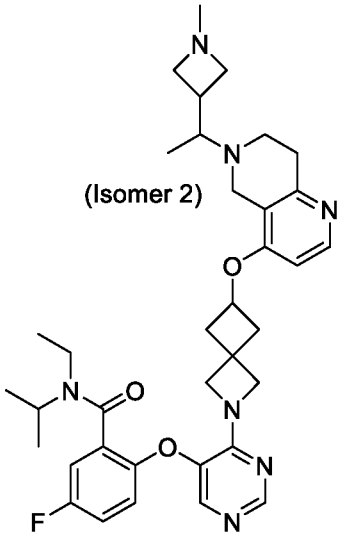
Step 5. (E2)-2-((4-(6-((6-(1-(Azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



In a 50 mL round bottom flask, *tert*-butyl *(E2)*-3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (170 mg, 0.233 mmol) was added in TFE (2 mL). TMSCl (101 mg, 0.932 mmol) was added to this solution at 0 °C. The reaction was stirred to RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure to obtain crude *(E2)*-2-((4-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

hydrochloride (0.145 g, 83% yield) as a solid. LCMS (Method G): Rt = 1.61 min, m/z = 630.2 $[M+H]^+$, 88.39%. This material was used without further purification.

Step 6. (E2)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

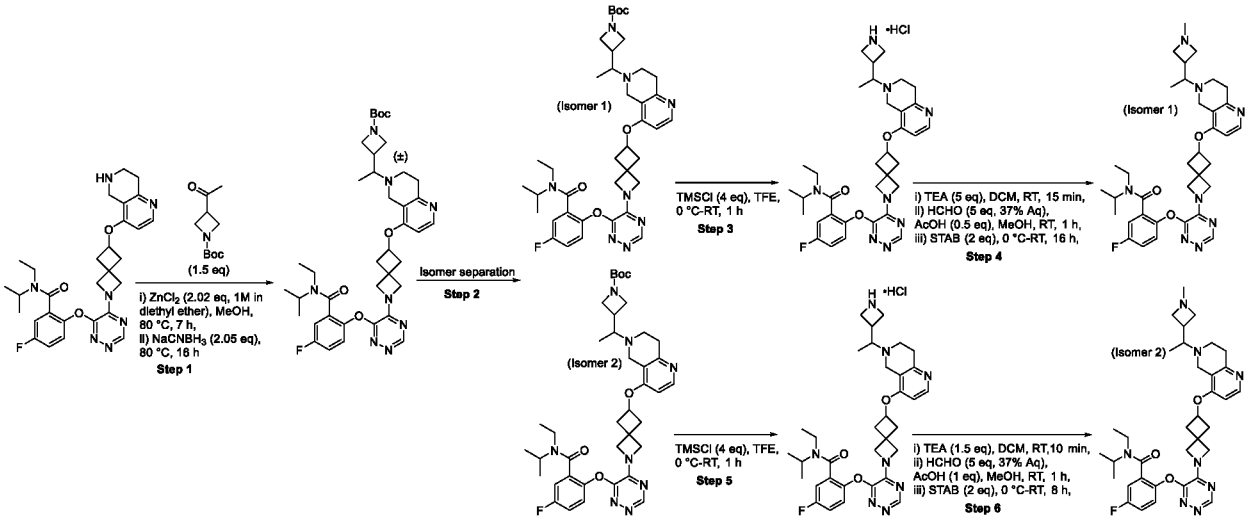


In a 250 mL round bottom flask under nitrogen atmosphere, *(E2)*-2-((4-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (0.145 g, 0.218 mmol) and TEA (0.110 g, 1.088 mmol) were added in DCM (2 mL). The reaction was stirred for 15 min and then concentrated under reduced pressure. The residue was taken up in MeOH (2 mL), and formaldehyde (0.088 g, 1.088 mmol, 37% in H_2O) and AcOH (6.53 mg, 0.109 mmol) were added at RT. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (0.092 g, 0.435 mmol) was added at 0 °C and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by achiral Prep SFC (Method U). The product fractions were concentrated under reduced pressure and lyophilized to afford *(E2)*-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.051 g, 35.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.16 (d, *J* =

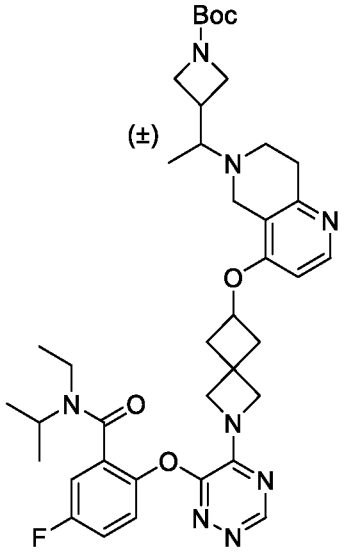
5.5 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 6.99 (m, 1H), 6.67 - 6.61 (m, 1H), 4.78 - 4.68 (m, 1H), 4.46 - 4.08 (m, 4H), 3.79 - 3.69 (m, 1H), 3.47 (s, 2H), 3.42 - 3.35 (m, 1H), 3.27 - 3.13 (m, 2H), 2.92 - 2.85 (m, 1H), 2.83 - 2.72 (m, 6H), 2.70 - 2.66 (m, 1H), 2.62 - 2.56 (m, 1H), 2.30 - 2.22 (m, 2H), 2.18 (s, 3H), 1.26 - 0.98 (m, 9H), 0.88 (d, J = 6.4 Hz, 3H), two proton merged with solvent peaks; LCMS (Method G): Rt = 1.59 min, m/z = 644.2 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 98.27%; Chiral SFC (Method K): Rt = 5.95 min, 99.44%.

Example 378. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 395)

Example 379. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 396)



Step 1. (±)-tert-Butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate

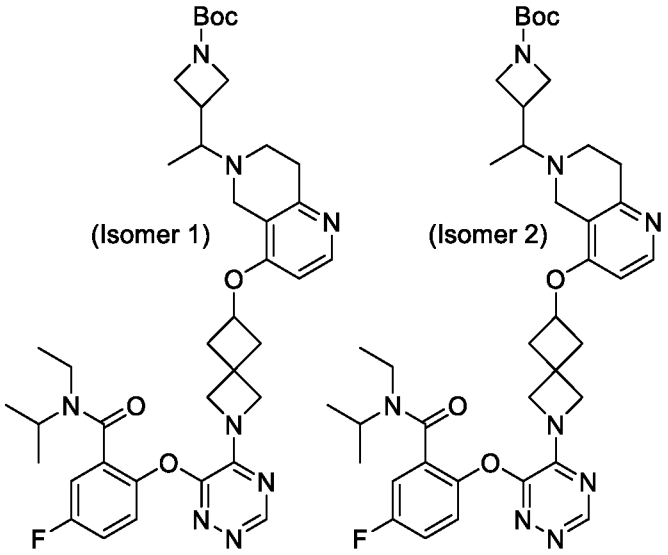


This compound was synthesized following the procedure described for the synthesis of Example 376 and 377, step 1, starting with 1 equivalent of *tert*-butyl 3-acetylazetidine-1-carboxylate, except that 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to afford (±)-*tert*-butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate as a solid.

Yield: 30.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.49 - 7.32 (m, 3H), 6.68 (d, J = 5.8 Hz, 1H), 4.84 - 4.74 (m, 1H), 4.69 - 4.49 (m, 2H), 4.34 - 4.11 (m, 2H), 3.93 - 3.73 (m, 3H), 3.67 - 3.59 (m, 2H), 3.56 - 3.36 (m, 4H), 3.13 - 2.89 (m, 2H), 2.87 - 2.71 (m, 5H), 2.61 - 2.54 (m, 1H), 2.31 - 2.24 (m, 1H), 1.37 (s, 9H), 1.16 - 0.65 (m, 12H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.05 min, m/z = 731.2 $[M+H]^+$, 99.36%; Chiral SFC (Method AAB): Peak 1: Rt = 5.26 min, 50.12%; Peak 2: Rt = 7.24 min, 49.88%.

Step 2. (E1)-tert-Butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate and (E2)-tert-butyl 3-(1-(4-((2-(6-(2-

(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate

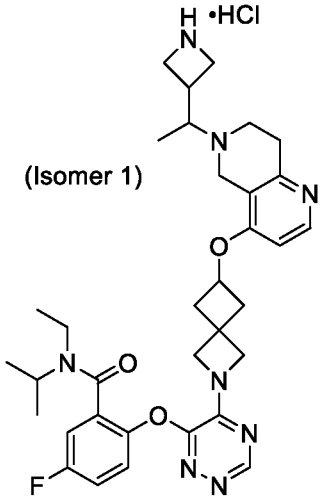


(±)-*tert*-Butyl 3-(1-(4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (500 mg) was purified by chiral Prep SFC (Method T). The product fractions were concentrated under reduced pressure to obtain both isomers, (*E1*)-*tert*-butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (120 mg, 39.5% yield) and (*E2*)-*tert*-butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate (130 mg, 42.6% yield).

Isomer 1. LCMS (Method B): Rt = 1.55 min, m/z = 731.6 $[M+H]^+$; HPLC (Method G): Rt = 6.30 min, 99.40%; Chiral SFC (Method AAB): Rt = 4.41 min, 100%.

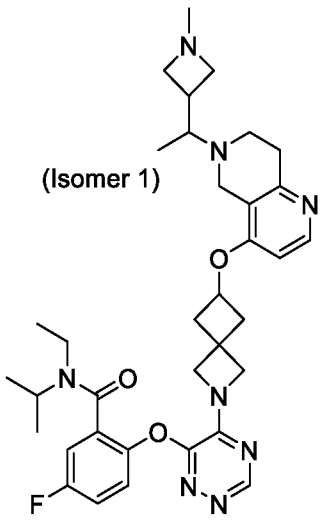
Isomer 2. LCMS (Method B): Rt = 1.52 min, m/z = 731.6 $[M+H]^+$; HPLC (Method G): Rt = 6.31 min, 98.21%; Chiral SFC (Method AAB): Rt = 6.35 min, 100%.

Step 3. (E1)-2-((5-(6-((6-(1-(Azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 376, step 3, starting with 1 equivalent of *(E1)-tert*-butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate. After completion, the reaction was concentrated under reduced pressure and the crude was re-concentrated from EtOAc (2 x 5 mL). The solid was dried under vacuum to obtain crude *(E1)*-2-((5-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride. This material was used without further purification.
Yield: Quantitative; LCMS (Method B): Rt = 1.08 min, m/z = 631.6 $[M+H]^+$, 99.54%.

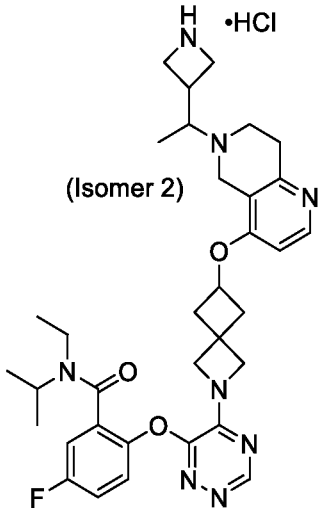
Step 4. (E1)-N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 376, step 4, starting with 1 equivalent of (*E1*)-2-((5-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 5 equivalents of TEA and 0.5 equivalent of AcOH were used. After completion, the reaction was diluted with cold water and the mixture was extracted with DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

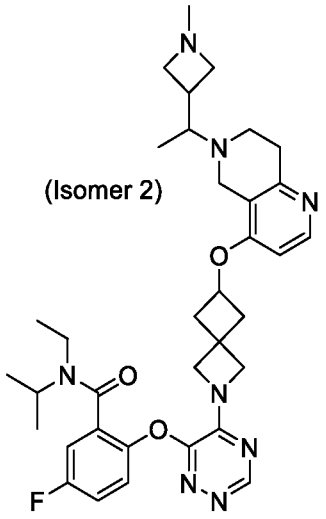
Yield: 46.0% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.49 - 7.32 (m, 3H), 6.67 (d, J = 5.7 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.67 - 4.50 (m, 2H), 4.34 - 4.12 (m, 2H), 3.68 - 3.57 (m, 1H), 3.54 - 3.39 (m, 3H), 3.16 - 2.99 (m, 1H), 2.93 - 2.71 (m, 7H), 2.66 - 2.55 (m, 2H), 2.36 - 2.31 (m, 2H), 2.16 (br s, 3H), 1.18 - 0.68 (m, 12H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.77 min, m/z = 645.4 $[M+H]^+$; HPLC (Method G): Rt = 4.49 min, 97.20%; Chiral SFC (Method K): Rt = 7.00 min, 97.02%.

Step 5. (E2)-2-((5-(6-((6-(1-(Azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 377, step 5, starting with 1 equivalent of (*E2*)-*tert*-butyl 3-(1-(4-((2-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)ethyl)azetidine-1-carboxylate. After completion, the reaction was concentrated under reduced pressure and the crude was re-concentrated from EtOAc. The residue was dried under vacuum to obtain crude (*E2*)-2-((5-(6-((6-(1-(zetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride as a sticky solid. This material was used without further purification. Yield: Quantitative; LCMS (Method B): Rt = 1.14 min, m/z = 631.6 $[M+H]^+$, 95.73%

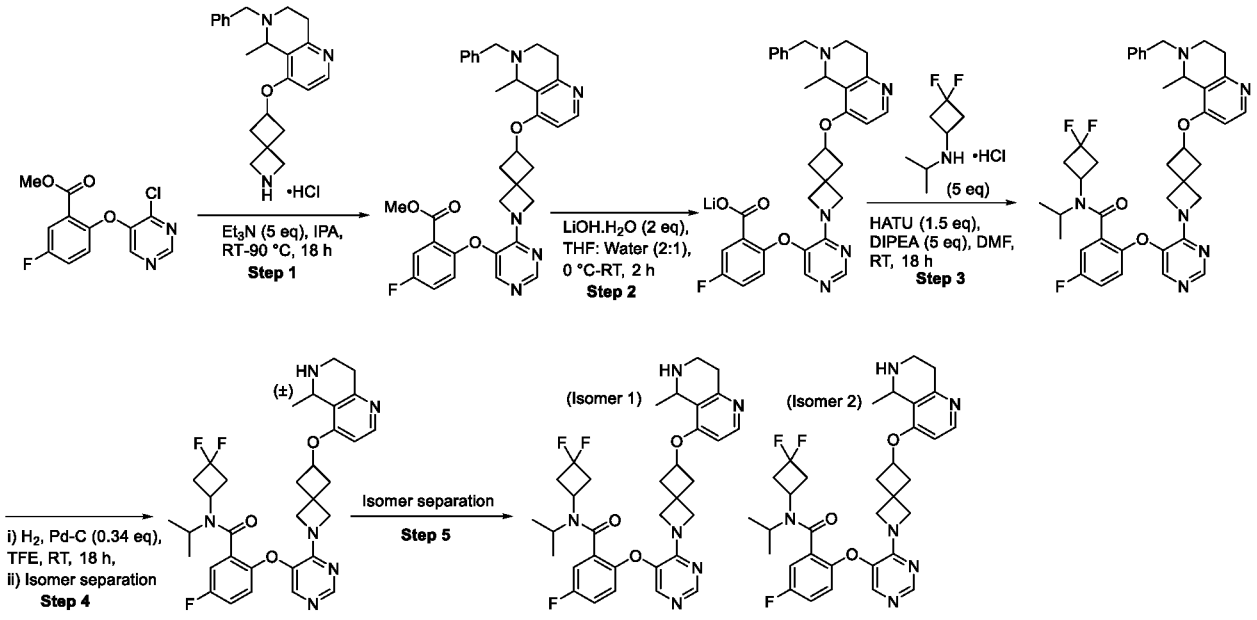
Step 6. (E2)-N-Ethyl-5-fluoro-N-isopropyl-2-((5-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



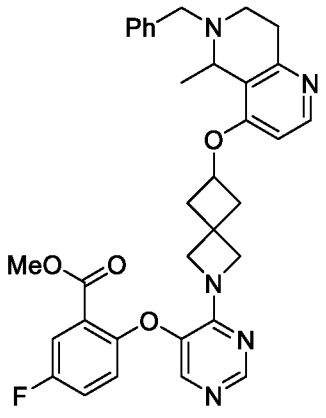
This compound was synthesized following the procedure described for the synthesis of Example 377, step 6, starting with 1 equivalent of (*E2*)-2-((5-(6-((6-(1-(azetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, except that 1.5 equivalents of TEA and 1 equivalent of AcOH were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(1-(1-methylazetidin-3-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid. Yield: 18.15%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.50 - 7.28 (m, 3H), 6.67 (d, J = 5.7 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.69 - 4.47 (m, 2H), 4.33 - 4.12 (m, 2H), 3.68 - 3.58 (m, 1H), 3.52 - 3.39 (m, 3H), 3.17 - 2.99 (m, 1H), 2.91 - 2.71 (m, 7H), 2.66 - 2.54 (m, 2H), 2.39 - 2.26 (m, 2H), 2.17 (br s, 3H), 1.17 - 0.66 (m, 12H), three protons merged with solvent peaks; LCMS (Method G): Rt = 1.66 min, m/z = 645.4 $[M+H]^+$; HPLC (Method G): Rt = 4.50 min, 99.05%; Chiral SFC (Method K): Rt = 6.99 min, 97.99%.

Example 380. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 308)

Example 381. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 309)



Step 1. (±)-Methyl 2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate

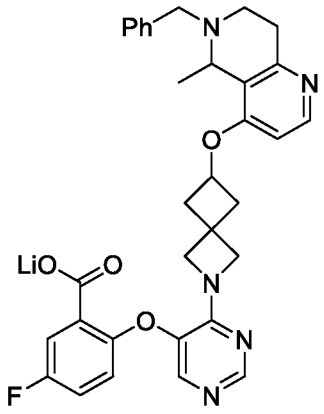


This compound was synthesized following the procedure described for the synthesis of Example 9, step 1, starting with 1 equivalent of methyl 2-((4-chloropyrimidin-5-yl)oxy)-5-fluorobenzoate, except that 1 equivalent of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride and 5 equivalents of Et_3N were used. The reaction was stirred at 90 °C. The reaction was concentrated under reduced

pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM) to afford (±)-methyl-2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate.

Yield: 52.9%; LCMS (Method D): Rt = 2.20 min, m/z = 596.2 $[M+H]^+$, 90.62%.

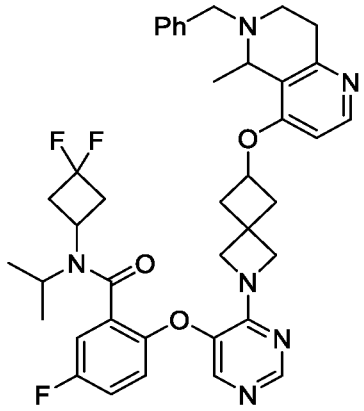
Step 2. (±)-Lithium 2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 2, starting with 1 equivalent of (±)-methyl 2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate, except that 2 equivalents of $LiOH.H_2O$ was used, and 2:1 THF/H_2O was used as the solvents. After completion, the reaction was concentrated under reduced pressure. The crude compound was re-concentrated from toluene to afford crude (±)-lithium 2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate. This material was used without further purification.

Yield: 71.4%; LCMS (Method G): Rt = 1.50 min, m/z = 582.3 $[M+H]^+$, 65.76%.

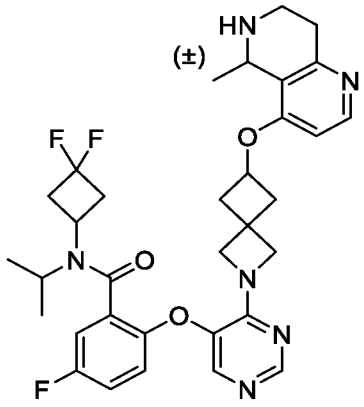
Step 3. (±)-2-((4-(6-((6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 5 equivalents of 3,3-difluoro-*N*-isopropylcyclobutan-1-amine hydrochloride, except that 1 equivalent of (±)-lithium 2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoate and 5 equivalents of DIPEA were used. After completion, the reaction was quenched with water and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 4% MeOH in DCM) to obtain (±)-2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide.

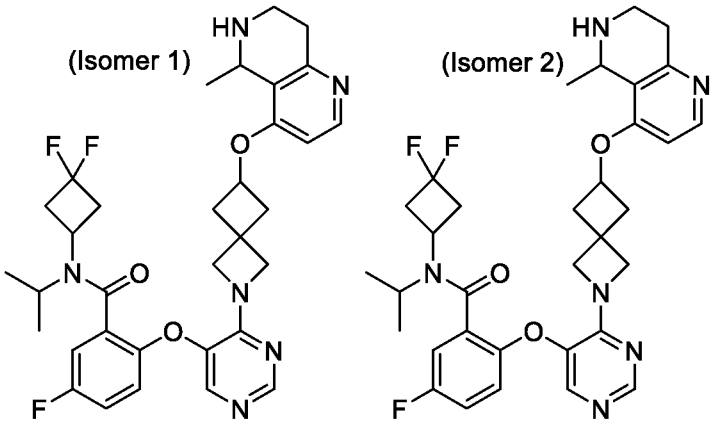
Yield: 41.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.21 (br d, J = 5.4 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.22 (m, 7H), 7.05 - 7.02 (m, 1H), 6.70 (br d, J = 5.4 Hz, 1H), 4.75 (quin, J = 6.3 Hz, 1H), 4.32 - 3.85 (m, 6H), 3.79 - 3.43 (m, 5H), 3.11 - 2.97 (m, 1H), 2.94 - 2.58 (m, 7H), 2.27 - 2.13 (m, 2H), 1.31 - 1.21 (m, 3H), 1.15 - 0.95 (m, 6H); LCMS (Method B): Rt = 1.44 min, m/z = 713.3 $[M+H]^+$, 92.14%.

Step 4. (±)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



In a 50 mL round bottom flask under an argon atmosphere, (±)-2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (360 mg, 0.505 mmol) was added in 2,2,2-trifluoroethanol (8 mL). Pd/C (180 mg, 0.169 mmol) was added to this solution, and the reaction was stirred at RT for 18 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (2 x 25 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to obtain (±)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (180 mg, 55.9% yield) as a solid. LCMS (Method G): Rt = 1.86 min, m/z = 623.3 $[M+H]^+$; HPLC (Method A): Rt = 5.28 min, 97.68%; Chiral SFC (Method AH): Peak 1: Rt = 4.22 min, 48.60%; Peak 2: Rt = 5.11 min, 49.95%.

Step 5. (E1)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and (E2)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



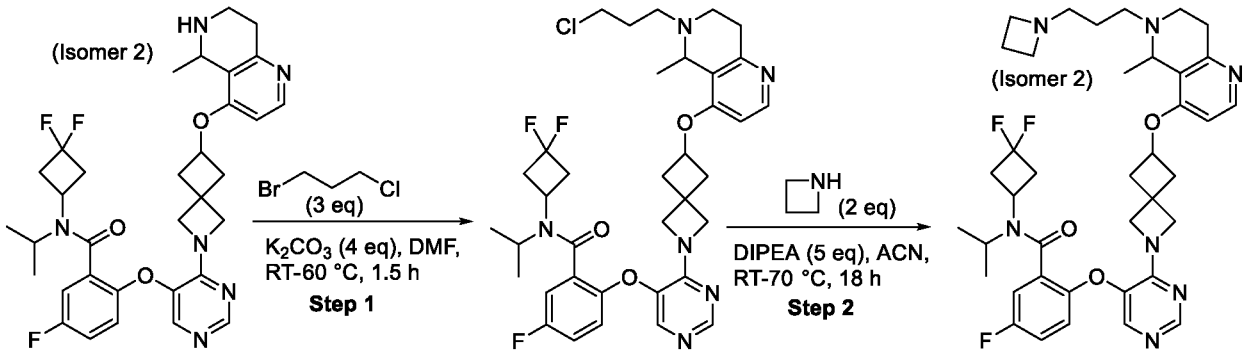
(±)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (180 mg) was purified by chiral Prep SFC (Method F) to obtain isomer 1 (72 mg) and isomer 2 (70 mg). ^{1}H NMR showed impurities in both separated compounds. Therefore, isomer 1 was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to obtain (*E1*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (31.69 mg, 17.38% yield) as a solid. Isomer 2 was re-purified by Prep HPLC (Method N) and the product fractions were concentrated under reduced pressure and lyophilized to obtain (*E2*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (30.24 mg, 16.61% yield) as a solid.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.15 (d, J = 5.7 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, J = 2.8, 8.1 Hz, 1H), 7.31 - 7.24 (m, 1H), 7.06 (dd, J = 4.2, 9.1Hz, 1H), 6.64 (d, J = 5.7 Hz, 1H), 4.73 (quin, J = 6.5 Hz, 1H), 4.32 - 4.00 (m, 6H), 3.97 - 3.86 (m, 1H), 3.78 - 3.45 (m, 3H), 3.12 - 3.02 (m, 1H), 2.94 - 2.88 (m, 1H), 2.83 - 2.58 (m, 6H), 2.29 - 2.19 (m, 2H), 1.28 (d, J = 6.6 Hz, 3H), 1.17 -0.92 (m, 6H); LCMS (Method G): Rt = 1.90 min, m/z = 623.5 $[M+H]^+$; HPLC (Method A): Rt = 5.06 min, 98.74%; Chiral SFC (Method AH): Rt = 4.46 min, 99.83%.

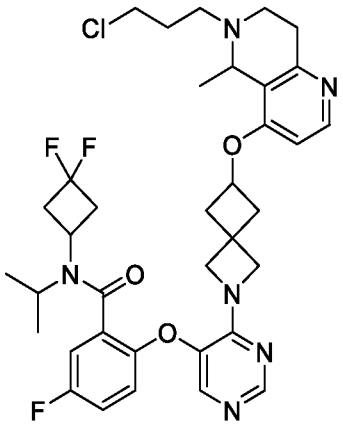
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, J = 2.9, 8.3 Hz, 1H), 7.31 - 7.18 (m, 1H), 7.06 (dd, J = 4.4, 9.1Hz, 1H), 6.64

(d, *J* = 5.6 Hz, 1H), 4.73 (quin, *J* = 6.4 Hz, 1H), 4.32 - 4.02 (m, 6H), 3.96 - 3.84 (m, 1H), 3.80 - 3.47 (m, 3H), 3.12 - 3.02 (m, 1H), 2.94 - 2. 87 (m, 1H), 2.84 - 2.58 (m, 6H), 2.28 - 2.19 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.16 - 0.96 (m, 6H); LCMS (Method G): Rt = 1.85 min, m/z = 623.3 $[M+H]^+$; HPLC (Method A): Rt = 5.07 min, 99.85%; Chiral SFC (Method AH): Rt = 5.32 min, 99.35%.

Example 382. ***(E2)*-2-((4-(6-((6-(3-(Azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide** (Compound No. 327)



Step 1. (E2)-2-((4-(6-((6-(3-Chloropropyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

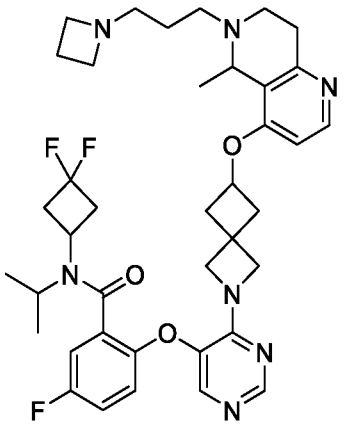


This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of *(E2)*-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-

methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide was used. The reaction was stirred in a pressure vial. *(E2)*-2-((4-(6-((6-(3-Chloropropyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide was obtained as a solid.

Yield: 62.2%; LCMS (Method G): Rt = 2.23 min, m/z = 699.4 $[M+H]^+$, 69.15%.

Step 2. (E2)-2-((4-(6-((6-(3-(Azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide



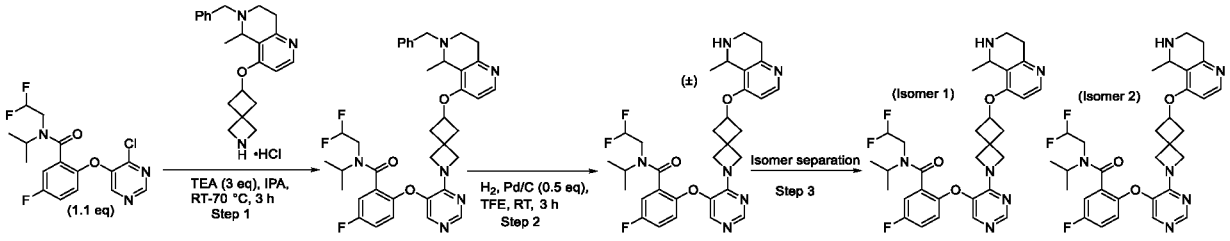
This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2 equivalents of azetidine, except that 1 equivalent *(E2)*-2-((4-(6-((6-(3-chloropropyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide was used. The reaction was stirred at 70 °C in a pressure vial. The reaction was concentrated under reduced pressure and re-concentrated from EtOAc. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method H). The product fractions were concentrated under reduced pressure and lyophilized to obtain *(E2)*-2-((4-(6-((6-(3-(azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 5.64%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, *J* = 2.8, 8.1 Hz, 1H), 7.31 - 7.24 (m, 1H), 7.06 (dd, *J* = 4.2, 9.1 Hz, 1H),

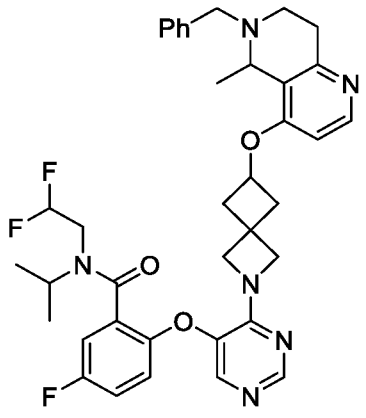
6.65 (d, *J* = 5.5 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.32 - 4.08 (m, 4H), 3.97 - 3.86 (m, 2H), 3.80 - 3.67 (m, 2H), 3.57 - 3.48 (m, 1H), 3.05 (t, *J* = 6.9 Hz, 4H), 2.99 - 2.89 (m, 1H), 2.88 - 2.70 (m, 5H), 2.63 - 2.55 (m, 2H), 2.44 - 2.33 (m, 3H), 2.29 - 2.20 (m, 2H), 1.97 - 1.88 (m, 2H), 1.48 - 1.36 (m, 2H), 1.19 - 0.98 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.09 min, m/z = 720.6 $[M+H]^+$; HPLC (Method A): Rt = 5.39 min, 93.94%; Chiral SFC (Method AH): Rt = 9.53 min, 100%.

Example 383. (*E1*)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 339)

Example 384. (*E2*)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 340)

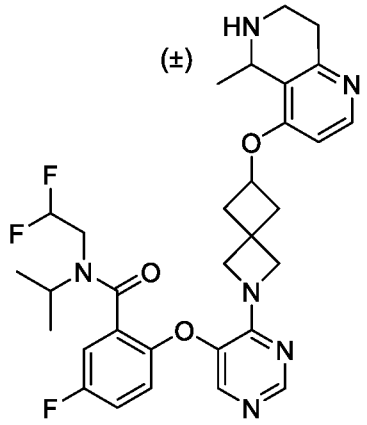


Step 1. (±)-2-((4-(6-((6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1 equivalent of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride and 1.1 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of TEA was used. The reaction was stirred in a pressure vial at 70 °C. After completion, the reaction was diluted with ice water and the mixture was extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 8% MeOH in DCM) to obtain (±)-2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (1.06 g, 36.3% yield) as a solid. LCMS (Method G): Rt = 2.28 min, m/z = 687.6 $[M+H]^+$, 61.57%.

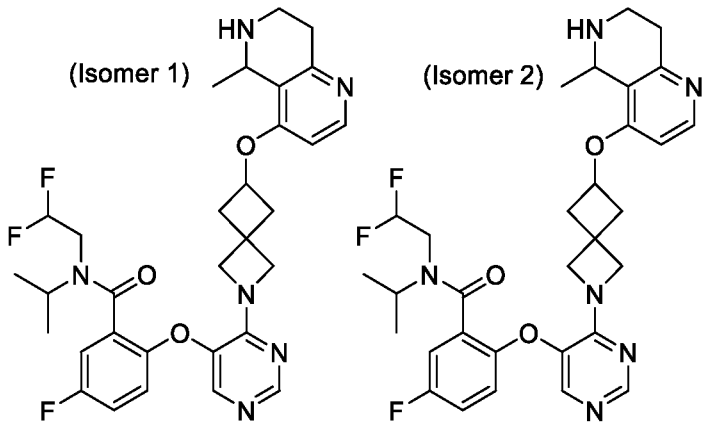
Step 2. (±)-N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (1.06 g, 1.543 mmol) in TFE (10 mL), Pd/C (0.821 g, 0.772 mmol) was added at RT, and the reaction was stirred at the same temperature for 3 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (200 mL). The filtrate was

concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by achiral Prep SFC (Method N). The product fractions were concentrated under reduced pressure to obtain (±)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.26 g, 28.0% yield) as a solid. LCMS (Method G): Rt = 1.71 min, m/z = 597.5 $[M+H]^+$; HPLC (Method A): Rt = 5.02 min, 98.14%; Chiral SFC (Method AZ): Peak 1: Rt = 6.27 min, 48.98%; Peak 2: Rt = 7.39 min, 49.70%.

Step 3. (E1)-N-(2,2-Difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and (E2)-N-(2,2-difluoroethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



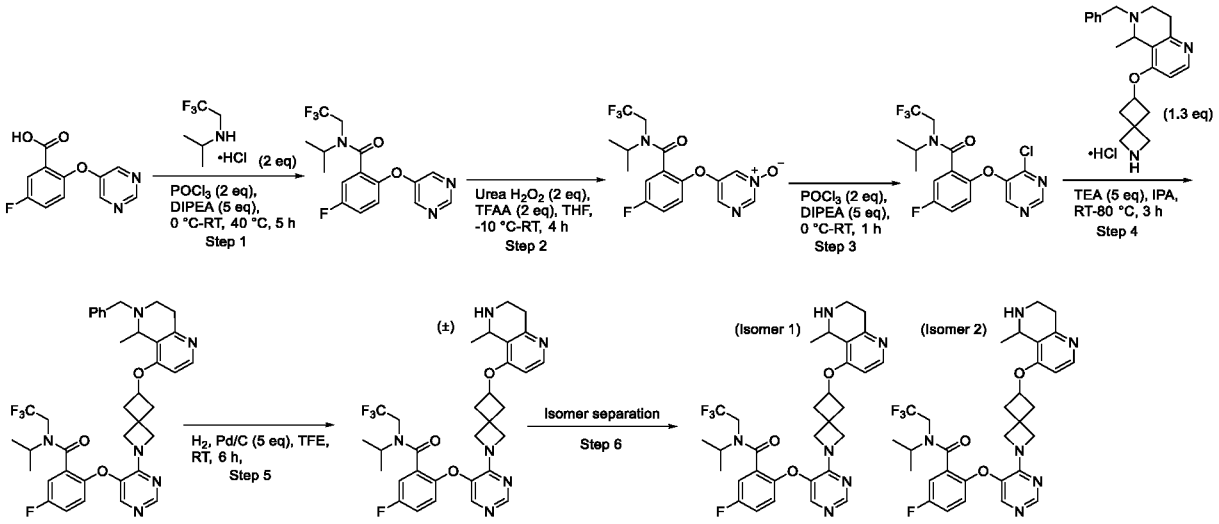
(±)-*N*-(2,2-Difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (260 mg, 0.436 mmol) was purified by chiral Prep SFC (Method Q). Both fractions were concentrated under reduced pressure and lyophilized to obtain both isomers, *(E1)-N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.07 g, 26.7% yield) and *(E2)-N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (0.06 g, 22.85% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 - 8.26 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.83 - 7.68 (m, 1H), 7.35 (dd, J = 3.1, 8.2 Hz, 1H), 7.29 (dt, J = 3.0, 8.6 Hz, 1H), 7.02 (dd, J = 4.4, 9.1Hz, 1H), 6.64 (d, J = 5.6 Hz, 1H), 6.39 - 6.05 (m, 1H), 4.77 - 4.67 (m, 1H), 4.29 - 4.13 (m, 3H), 4.13 - 4.01 (m, 2H), 3.91 - 3.64 (m, 3H), 3.12 - 3.03 (m, 1H), 2.93 - 2.85 (m, 1H), 2.83 - 2.72 (m, 2H), 2.69 - 2.58 (m, 2H), 2.28 - 2.18 (m, 3H), 1.27 (br d, J = 6.6 Hz, 3H), 1.25 - 1.03 (m, 6H); LCMS (Method G): Rt = 1.75 min, m/z = 597.5 $[M+H]^+$; HPLC (Method A): Rt = 5.08 min, 99.40%; Chiral SFC (Method AZ): Rt = 6.49 min, 98.64%.

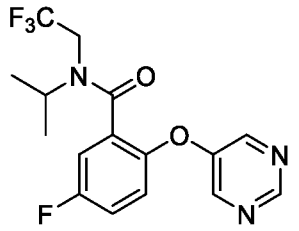
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.27 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.83 - 7.67 (m, 1H),
7.35 (dd, J = 3.1, 8.2 Hz, 1H), 7.29 (dt, J = 3.1, 8.6 Hz, 1H), 7.02 (dd, J = 4.3, 9.1Hz, 1H), 6.64 (d, J = 5.6 Hz, 1H), 6.40 - 6.05 (m, 1H), 4.77 - 4.65 (m, 1H), 4.27 - 4.13 (m, 3H), 4.13 - 4.01 (m, 2H), 3.90 - 3.64 (m, 3H), 3.12 - 3.02 (m, 1H), 2.93 - 2.85 (m, 1H), 2.83 - 2.73 (m, 2H), 2.70 - 2.59 (m, 2H), 2.30 - 2.15 (m, 3H), 1.27 (d, J = 6.5 Hz, 3H), 1.25 - 1.04 (m, 6H); LCMS (Method G): Rt = 1.74 min, m/z = 597.5 $[M+H]^+$; HPLC (Method A): Rt = 5.10 min, 99.34%; Chiral SFC (Method AZ): Rt = 7.60 min, 97.51%

Example 385. (*E1*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 397)

Example 386. (*E2*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 398)



Step 1. 5-Fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)-N-(2,2,2-trifluoroethyl)benzamide

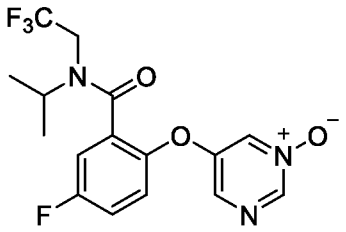


The reaction was performed following the same procedure in two batches (2 x 5 g).

In a dried, 1000 mL three neck round bottom flask under a nitrogen atmosphere, 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid (5.0 g, 21.35 mmol) and *N*-(2,2,2-trifluoroethyl)propan-2-amine hydrochloride (7.58 g, 42.7 mmol) were added in DCM (150 mL) at 0 °C. To this solution, DIPEA (18.65 mL, 107 mmol) and $POCl_3$ (3.99 mL, 42.7 mmol) were added at 0 °C. The reaction was stirred at 40 °C for 5 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). The reaction mixtures from both batches were combined for work-up and purification. The reaction was diluted with water (100 mL) and the mixture was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 42% EtOAc in hexane) to obtain 5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(2,2,2-trifluoroethyl)benzamide (1.32 g,

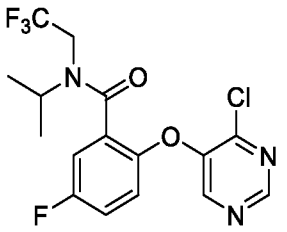
11.74% combined yield) as a liquid. LCMS (Method G): Rt = 1.91 min, m/z = 358.1 $[M+H]^+$, 85.68%.

Step 2. 5-(4-Fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidine 1-oxide



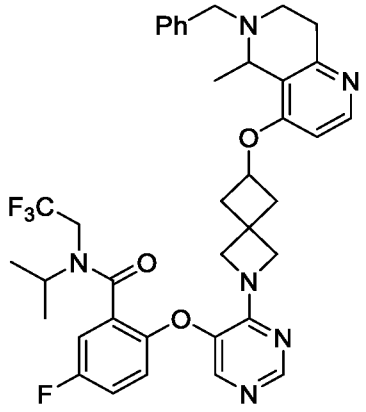
This compound was synthesized following the procedure described for the synthesis of Intermediate 26, step 3, starting with 5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(2,2,2-trifluoroethyl)benzamide, to obtain crude 5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidine 1-oxide a gummy solid.
Yield: 88%; LCMS (Method G): Rt = 1.73 min, m/z = 374.2 $[M+H]^+$, 93.59%. This material was used without further purification.

Step 3. 2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 26, step 4, starting with 5-(4-fluoro-2-(isopropyl(2,2,2-trifluoroethyl)carbamoyl)phenoxy)pyrimidine 1-oxide, to obtain 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide as a liquid.
Yield: 58.7%; LCMS (Method G): Rt = 2.14 min, m/z = 392.2 $[M+H]^+$, 99.47%.

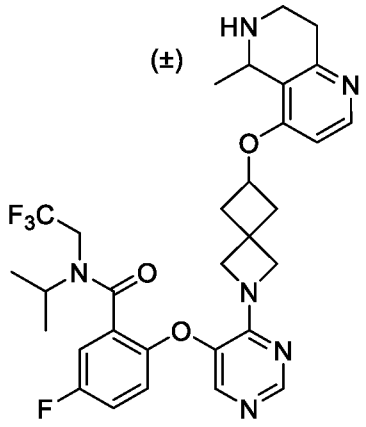
Step 4. (±)-2-((4-(6-((6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(2,2,2-trifluoroethyl)benzamide



The reaction was performed following the same procedure in two batches (450 mg and 800 mg).

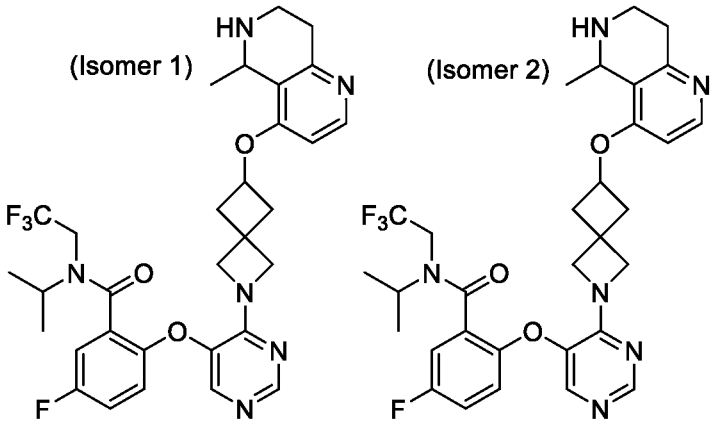
In a 100 mL round bottom flask under a nitrogen atmosphere, (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (1.025 g, 2.65 mmol) was added in IPA (15 mL). To this solution, 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (0.8 g, 2.042 mmol) and TEA (1.435 mL, 10.21 mmol) were added at RT. The reaction was stirred 80 °C for 3 h. The reaction progress was monitored by TLC (5% MeOH in DCM). The reaction mixtures from batches were combined for work up and purification. Water (30 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 5% MeOH in DCM), then by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (650 mg, 20.72% combined yield) as a solid. LCMS (Method G): Rt = 2.22 min, m/z = 705.3 $[M+H]^+$, 71.70%.

Step 5. (±)-5-Fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide



To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (650 mg, 0.922 mmol) in TFE (13 mL), dry Pd/C (491 mg, 4.61 mmol) was added at RT. The reaction was stirred under a hydrogen atmosphere (balloon pressure) for 6 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 30 mL). The filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to afford (±)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (420 mg, 71.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.36 - 7.27 (m, 2H), 7.03 (dd, J = 4.4, 9.0 Hz, 1H), 6.63 (d, J = 5.6 Hz, 1H), 4.72 (quin, J = 6.4 Hz, 1H), 4.34 - 4.13 (m, 5H), 4.06 - 3.89 (m, 3H), 3.12 - 3.03 (m, 1H), 2.93 - 2.85 (m, 1H), 2.83 - 2.72 (m, 2H), 2.70 - 2.62 (m, 2H), 2.28 - 2.18 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H), 1.25 - 1.01 (m, 6H), one proton merged with solvent peaks; LCMS (Method F): Rt = 1.98 min, m/z = 615.3 $[M+H]^+$; HPLC (Method A): Rt = 5.17 min, 94.34%; Chiral SFC (Method AF): Peak 1: Rt = 5.19 min, 48.86%; Peak 2: Rt = 6.12 min, 50.23%.

Step 6. (E1)-5-Fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide and (E2)-5-Fluoro-N-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(2,2,2-trifluoroethyl)benzamide

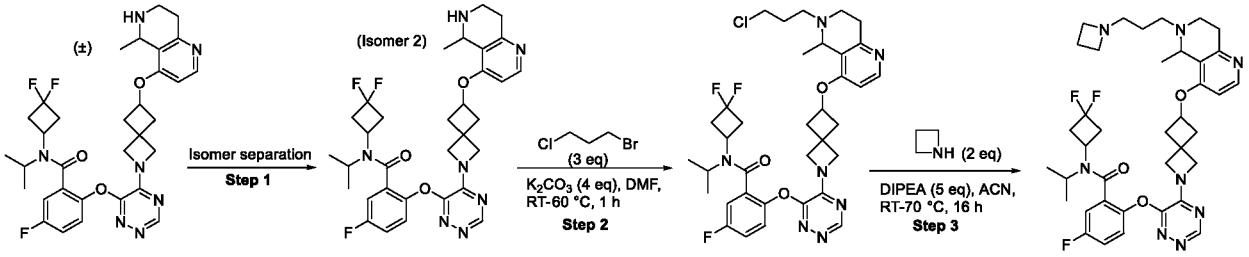


(±)-5-Fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (420 mg, 0.683 mmol) was purified by chiral Prep HPLC (Method R) to obtain both isomers, (*E1*)-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (135.87 mg, 31.5% yield) as a solid, and isomer 2 (*E2*). Isomer 2 was impure. Therefore, it was re-purified by Prep HPLC (Method C). The product fractions were concentrated under reduced pressure and lyophilized to afford *(E2)*-5-fluoro-*N*-isopropyl-2-((4-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (100.36 mg, 23.62% yield) as a solid.

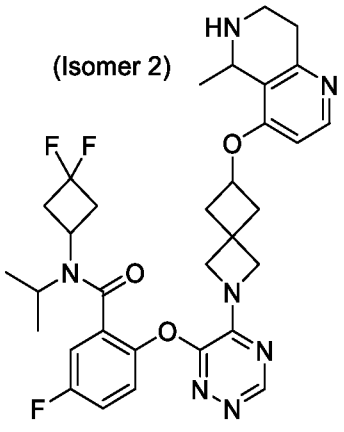
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.37 – 7.27 (m, 2H), 7.03 (dd, J = 4.3, 8.9 Hz, 1H), 6.63 (d, J = 5.6 Hz, 1H), 4.72 (quin, J = 6.3 Hz, 1H), 4.35 – 4.13 (m, 5H), 4.12 – 3.88 (m, 3H), 3.12 – 3.02 (m, 1H), 2.93 – 2.85 (m, 1H), 2.83 – 2.71 (m, 2H), 2.70 – 2.59 (m, 2H), 2.29 – 2.16 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H), 1.25 – 1.05 (m, 6H), one proton merged with solvent peaks; LCMS (Method A): Rt = 2.27 min, m/z = 615.2 $[M+H]^+$; HPLC (Method A): Rt = 5.17 min, 96.66%; Chiral SFC (Method AF): Rt = 5.02 min, 96.95%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.80 (s, 1H), 7.36 – 7.26 (m, 2H), 7.03 (dd, J = 4.3, 8.9 Hz, 1H), 6.63 (d, J = 5.8 Hz, 1H), 4.72 (quin, J = 6.3 Hz, 1H), 4.34 – 4.12 (m, 5H), 4.11 – 3.87 (m, 3H), 3.12 – 3.02 (m, 1H), 2.94 – 2.85 (m, 1H), 2.82 – 2.71 (m, 2H), 2.70 – 2.59 (m, 2H), 2.27 – 2.17 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H), 1.25 – 1.05 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.66 min, m/z = 615.1 $[M+H]^+$; HPLC (Method A): Rt = 5.21 min, 99.83%; Chiral SFC (Method AF): Rt = 6.23 min, 98.55%.

Example 287. (*E2*)-2-((5-(6-((6-(3-(Azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 336)



Step 1. (E2)-N-(3,3-Difluorocyclobutyl)-5-fluoro-N-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



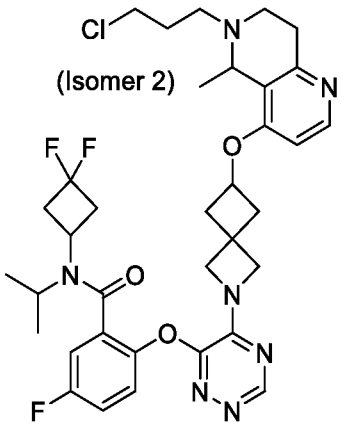
(±)-*N*-(3,3-Difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was synthesized following the procedure described for the synthesis of Example 66. The

compound was purified by chiral Prep SFC (Method P) to obtain peak 2, (*E2*)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide as a solid.

Yield: 35.0%; LCMS (Method G): Rt = 1.67 min, m/z = 624.2 $[M+H]^+$; HPLC (Method A): Rt = 5.15 min, 96.64%; Chiral SFC (Method AX): Rt = 4.44 min, 98.82%.

Note: Peak 1 was not isolated.

Step 2. (E2)-2-((5-(6-((6-(3-Chloropropyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

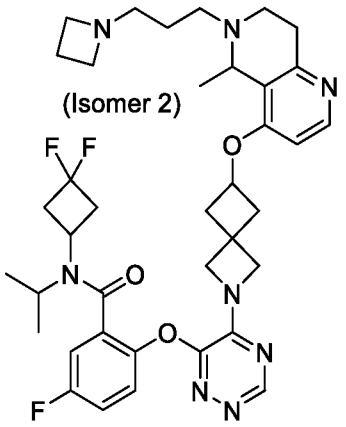


The reaction was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Intermediate 50, procedure 3, starting with 3 equivalents of 1-bromo-3-chloropropane, except that 1 equivalent of *(E2)-N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide was used. The reaction was performed in a pressure vial. The reaction mixtures from both batches were combined and worked up. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain (*E2*)-2-((5-(6-((6-(3-chloropropyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Combined yield: 26.29%; LCMS (Method G): Rt = 2.14 min, m/z = 700.6 $[M+H]^+$, 93.13%.

Step 3. (E2)-2-((5-(6-((6-(3-(Azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

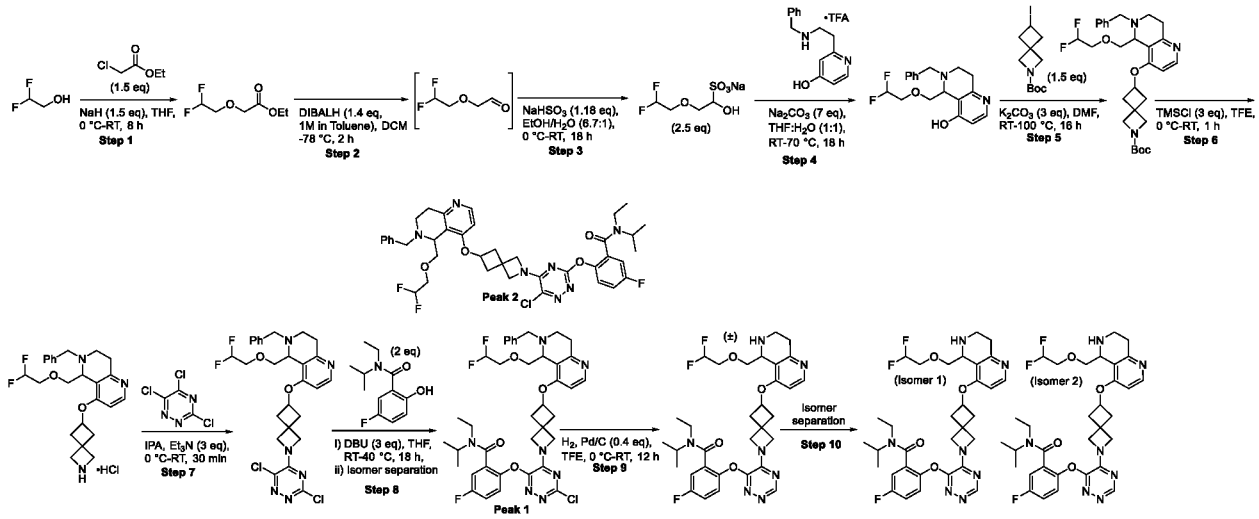


This compound was synthesized following the procedure described for the synthesis of Example 23, step 2, starting with 2 equivalents of azetidine, except that 1 equivalent of *(E2)*-2-((5-(6-((6-(3-chloropropyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide was used. The reaction was stirred at 70 °C in a pressure vial. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), and then by Prep HPLC (Method V). The product fractions were concentrated under reduced pressure to afford *(E2)*-2-((5-(6-((6-(3-(azetidin-1-yl)propyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

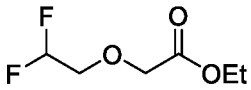
Yield: 14.28%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.50 - 7.35 (m, 3H), 6.72 - 6.61 (m, 1H), 4.79 (quin, J = 6.5 Hz, 1H), 4.69 - 4.49 (m, 2H), 4.30 - 4.12 (m, 2H), 4.00 - 3.79 (m, 2H), 3.63 (br s, 2H), 3.11 - 2.99 (m, 4H), 2.99 - 2.91 (m, 1H), 2.89 - 2.73 (m, 5H), 2.63 - 2.56 (m, 2H), 2.45 - 2.24 (m, 6H), 1.98 - 1.84 (m, 2H), 1.41 (br s, 2H), 1.16 (br d, J = 5.5 Hz, 3H), 1.12 - 0.63 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.87 min, m/z = 721.7 $[M+H]^+$; HPLC (Method A): Rt = 5.42 min, 98.20%; Chiral SFC (Method AY): Rt = 1.21 min, 95.40%.

Example 388. (*E1*)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 399)

Example 389. (*E2*)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 400)



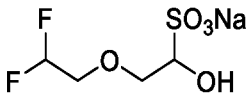
Step 1. Ethyl 2-(2,2-difluoroethoxy)acetate



To a stirred solution of 2,2-difluoroethan-1-ol (5.0 g, 60.9 mmol) in THF (60 mL), NaH (3.66 g, 91 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred for 10 min at the same temperature. To this reaction mixture, ethyl 2-chloroacetate (11.20 g, 91 mmol) was added at 0 °C and the reaction was stirred at RT for 8 h. The reaction was monitored by ^{1}H NMR. The reaction was quenched with water (100 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford crude ethyl 2-(2,2-difluoroethoxy)acetate (7.23 g, 70.6% yield) as a liquid. This material was used without further purification. ^{1}H NMR (400 MHz,

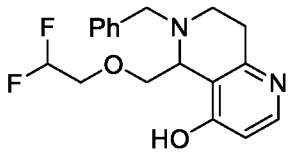
DMSO-d_6): δ 6.33 - 6.01 (m, 1H), 4.23 (s, 2H), 4.20 - 4.11 (m, 2H), 3.79 (dt, J = 3.8, 15.1 Hz, 2H), 1.25 - 1.19 (m, 3H).

Step 2 and 3. Sodium 2-(2,2-difluoroethoxy)-1-hydroxyethane-1-sulfonate



In a dried, 250 mL two neck round bottom flask under a nitrogen atmosphere, ethyl 2-(2,2-difluoroethoxy)acetate (3.7 g, 22.01 mmol) was added in DCM (74 mL). To this solution, DIBAL-H (30.8 mL, 30.8 mmol, 1M in toluene) was added at -78 °C and the reaction was stirred for 2 h at the same temperature. The reaction progress was monitored by TLC (10% EtOAc in hexane). The reaction was quenched with saturated potassium sodium tartrate tetrahydrate (5 mL) and diluted with water (20 mL), and the mixture was extracted with DCM (2 x 30 mL). The combined organic layer was washed with brine (50 mL). The organic layer was transferred to a 250 mL round bottom flask. To this solution, sodium bisulfite (2.290 g, 22.01 mmol), ethanol (60 mL), and water (9 mL) were added at 0 °C. The reaction was stirred at RT for 18 h. The reaction was filtered through a Celite® pad, and the pad was washed with DCM (3 x 30 mL). The filtrate was concentrated under reduced pressure to obtain crude sodium 2-(2,2-difluoroethoxy)-1-hydroxyethane-1-sulfonate (2.7 g, 53.8% yield) as a solid. This material was used without further purification.

Step 4. (±)-6-Benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol

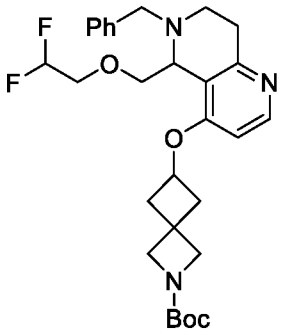


Step 3 was performed following the same procedure in two batches, (2 x 750 mg).

To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (750 mg, 2.298 mmol) and sodium 2-(2,2-difluoroethoxy)-1-hydroxyethane-1-sulfonate (1311 mg, 5.75 mmol) in 1:1 THF/H_2O (10 mL), sodium carbonate (1705 mg, 16.09 mmol) was added

at RT. The reaction was stirred at 70 °C for 18 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction mixtures from both batches were combined for work-up and purification. The reaction was diluted with water (20 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 10% MeOH in DCM) to obtain (±)-6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (605 mg, 30.06% combined yield) as a sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.32 (br d, J = 4.3 Hz, 1H), 7.53 (dd, J = 5.7, 7.2 Hz, 1H), 7.39 - 7.34 (m, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26 - 7.20 (m, 1H), 6.26 - 5.94 (m, 2H), 3.87 - 3.80 (m, 2H), 3.75 - 3.61 (m, 4H), 3.56 (dd, J = 1.9, 10.8 Hz, 1H), 2.82 - 2.66 (m, 2H), 2.37 - 2.26 (m, 1H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.65 min, m/z = 335.0 $[M+H]^+$, 76.32%.

Step 5. (±)-tert-Butyl 6-((6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

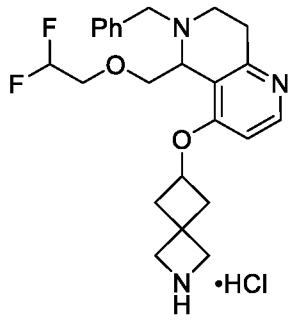


This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 1.5 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used. After completion, the reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product eluted at 4% MeOH in DCM) to afford (±)-

tert-butyl 6-((6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a solid.

Yield: 63.5% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 5.6 Hz, 1H), 7.39 - 7.21 (m, 5H), 6.70 (d, J = 5.8 Hz, 1H), 6.28 - 5.95 (m, 1H), 4.72 (quin, J = 6.6 Hz, 1H), 4.07 - 4.04 (m, 1H), 3.94 - 3.79 (m, 6H), 3.76 - 3.64 (m, 3H), 3.57 (dd, J = 2.1, 11.1 Hz, 1H), 3.28 - 3.19 (m, 1H), 2.95 - 2.67 (m, 4H), 2.60 - 2.55 (m, 1H), 2.23 - 2.11 (m, 2H), 1.37 (s, 9H); LCMS (Method B): Rt = 1.66 min, m/z = 530.5 $[M+H]^+$, 84.94%.

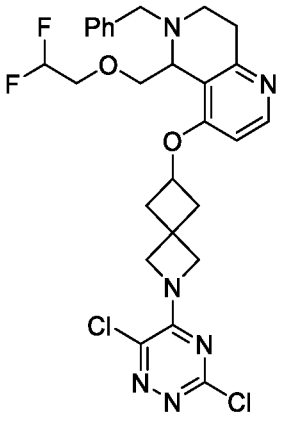
Step 6. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with 1 equivalent of (±)-*tert*-butyl 6-((6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, except that 3 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure and triturated with EtOAc. The organic layer was decanted and the solid was dried to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride as a solid. This material was used without further purification.

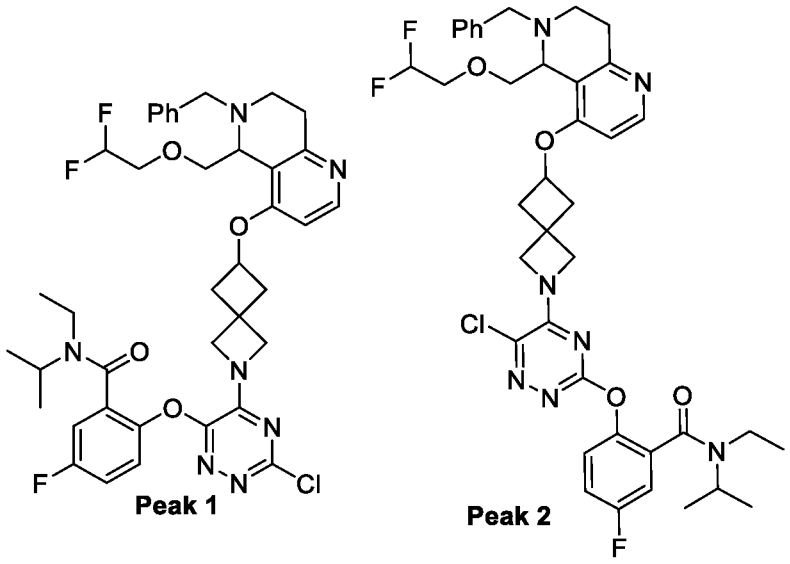
Yield: 85%; LCMS (Method G): Rt = 1.59 min, m/z = 430.0 $[M+H]^+$, 88.17%.

Step 7. (±)-6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine



To a stirred solution of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (750 mg, 1.610 mmol) in DCM (10 mL), TEA (0.679 mL, 4.83 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred for 10 min at the same temperature. To this reaction mixture, 3,5,6-trichloro-1,2,4-triazine (297 mg, 1.610 mmol) was added in one portion at the same temperature and the reaction was stirred at RT for 20 min. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with water (20 mL) and the mixture was extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (690 mg, 70.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 5.6 Hz, 1H), 7.41 - 7.22 (m, 5H), 6.72 (d, J = 5.8 Hz, 1H), 6.30 - 5.95 (m, 1H), 4.83 - 4.67 (m, 3H), 4.28 - 4.12 (m, 2H), 4.07 (br d, J = 6.5 Hz, 1H), 3.91 - 3.80 (m, 2H), 3.79 - 3.64 (m, 3H), 3.59 (br d, J = 11.0 Hz, 1H), 3.30 - 3.18 (m, 1H), 2.96 - 2.77 (m, 4H), 2.60 - 2.52 (m, 1H), 2.34 - 2.22 (m, 2H); LCMS (Method B): Rt = 1.58 min, m/z = 577.0 $[M+H]^+$, 94.60%.

Step 8. (±)-2-((5-(6-((6-Benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (±)-2-((5-(6-((6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



Step 8 was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 2 equivalents of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 1 equivalent of (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine and 3 equivalents of DBU were used. After work-up, the crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain a mixture of regioisomers as sticky solids. The crude products from both batches were combined and purified by achiral Prep SFC (Method I). The product fractions were concentrated under reduced pressure to obtain both regioisomers.

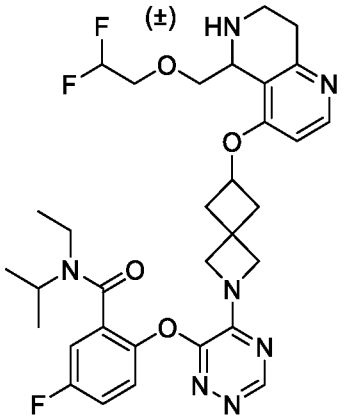
Peak 1. (±)-2-((5-(6-((6-Benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Combined yield: 41.92%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (t, J = 5.3 Hz, 1H), 7.49 - 7.19 (m, 8H), 6.76 -6.67 (m, 1H), 6.29 - 5.91 (m, 1H), 4.79 (quin, J = 6.5 Hz, 1H), 4.69 - 4.54 (m, 2H), 4.33 - 4.14 (m, 2H), 4.12 - 4.02 (m, 1H), 3.84 (br dd, J = 8.1, 14.3 Hz, 2H), 3.78 - 3.55 (m, 5H), 3.48 - 3.37 (m, 1H), 3.27 - 3.00 (m, 2H), 2.94 - 2.76 (m, 4H), 2.60 - 2.55 (m, 1H), 2.36 - 2.20 (m, 2H), 1.19 - 0.73 (m, 9H); LCMS (Method G): Rt = 2.24 min, m/z = 766.1 $[M+H]^+$, 96.94%.

Peak 2. (±)-2-((5-(6-((6-Benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Combined yield: 22.58%; LCMS (Method G): Rt = 2.30 min, m/z = 766.3 $[M+H]^+$, 99.89%.

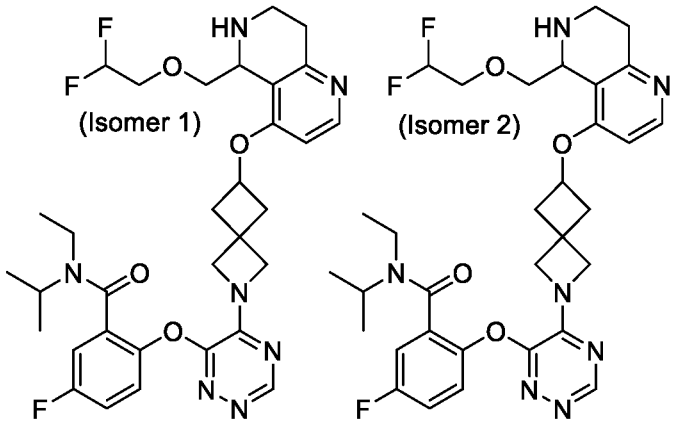
Step 9. (±)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



In a 50 mL round bottom flask under a nitrogen atmosphere, (±)-2-((5-(6-((6-benzyl-5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (300 mg, 0.392 mmol) was added in 2,2,2-trifluoroethanol (12 mL). To this solution, dry 10% Pd/C (167 mg, 0.157 mmol) was added at RT under a nitrogen atmosphere. The reaction was stirred for 12 h under a hydrogen atmosphere (balloon pressure). The reaction was monitored by TLC (10% MeOH in DCM). The reaction was bubbled with nitrogen gas for 2 min. The reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 25 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to obtain (±)-2-((5-(6-((5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (220 mg, 87% yield) as

a sticky solid. LCMS (Method G): Rt = 1.83 min, m/z = 642.4 $[M+H]^+$; HPLC (Method G): Rt = 4.85 min, 99.15%; Chiral SFC (Method AAL): Peak 1: Rt = 3.89 min, 49.87%; Peak 2: Rt = 4.88 min, 49.13%.

Step 10. (E1)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((5-(6-((5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



(±)-2-((5-(6-((5-((2,2-Difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (220 mg) was purified by chiral Prep SFC (Method AE). The product fractions were concentrated under reduced pressure and lyophilized to obtain (*E1*)-2-((5-(6-((5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (86.71 mg, 39.4 % yield) and (*E2*)-2-((5-(6-((5-((2,2-difluoroethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (81.03 mg, 36.6 % yield) as solids.

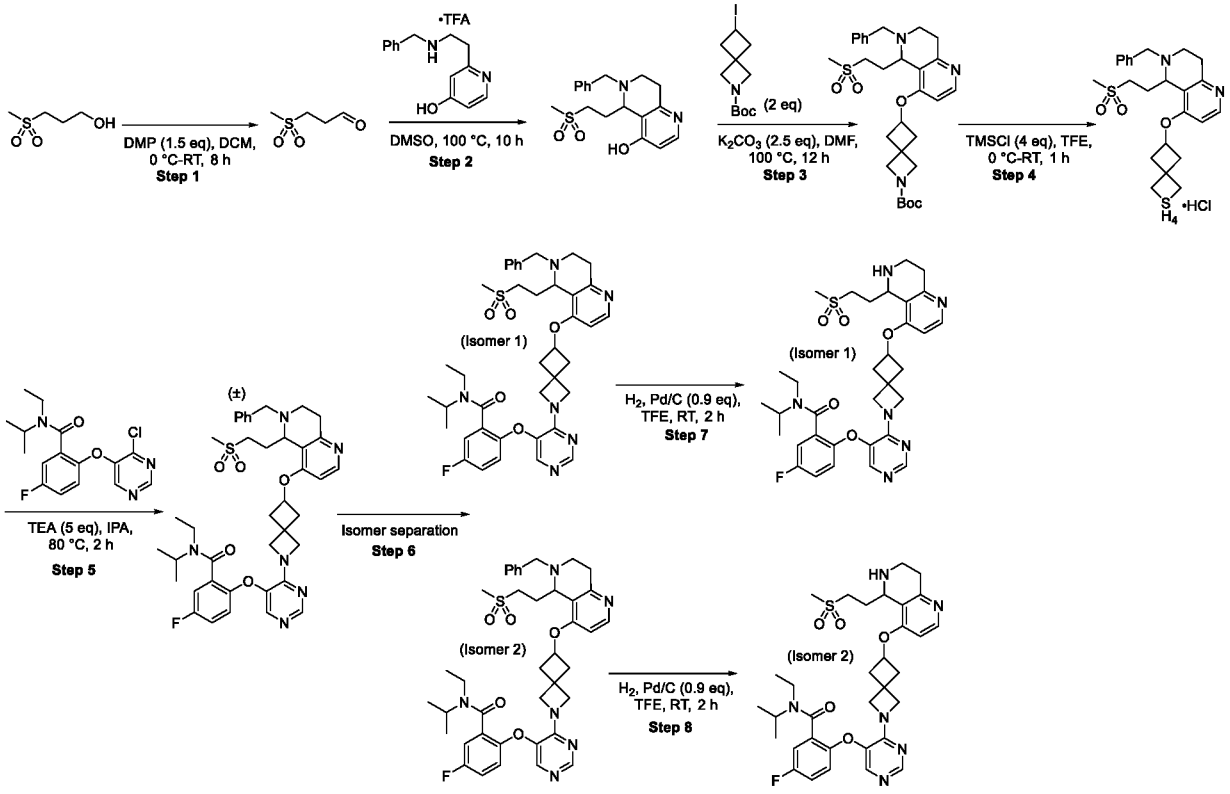
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.21 (d, J = 5.5 Hz, 1H), 7.48 - 7.32 (m, 3H), 6.70 (d, J = 5.6 Hz, 1H), 6.35 - 5.97 (m, 1H), 4.80 (quin, J = 6.6 Hz, 1H), 4.66 - 4.48 (m, 2H), 4.31 - 4.09 (m, 3H), 3.87 - 3.56 (m, 5H), 3.48 - 3.37 (m, 1H), 3.14 - 2.99 (m, 2H), 2.97 - 2.77 (m, 3H), 2.76 - 2.60 (m, 2H), 2.39 - 2.24 (m, 2H), 1.17 - 0.65 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.57 min, m/z = 642.2 $[M+H]^+$;

HPLC (Method G): Rt = 4.86 min, 99.91%; Chiral SFC (Method AAL): Rt = 4.18 min, 99.86%.

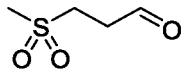
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.21 (d, J = 5.6 Hz, 1H), 7.48 - 7.30 (m, 3H), 6.70 (d, J = 5.6 Hz, 1H), 6.35 - 5.97 (m, 1H), 4.80 (quin, J = 6.5 Hz, 1H), 4.68 - 4.49 (m, 2H), 4.32 - 4.10 (m, 3H), 3.83 - 3.56 (m, 5H), 3.48 - 3.36 (m, 1H), 3.16 - 2.99 (m, 2H), 2.97 - 2.80 (m, 3H), 2.78 - 2.60 (m, 2H), 2.39 - 2.17 (m, 2H), 1.17 - 0.65 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.57 min, m/z = 642.2 $[M+H]^+$; HPLC (Method G): Rt = 4.86 min, 99.50%; Chiral SFC (Method AAL): Rt = 5.42 min, 98.99%.

Example 390. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 401)

Example 391. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 402)

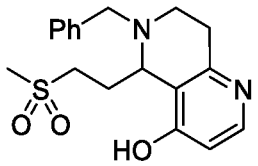


Step 1. 3-(Methylsulfonyl)propanal



In a 500 mL two neck dried round bottom flask under a nitrogen atmosphere, 3-(methylsulfonyl)propan-1-ol (8 g, 57.9 mmol) was added in DCM (120 mL). To this solution, Dess-Martin periodinane (36.8 g, 87 mmol) was added at 0 °C, and the reaction was stirred at RT for 8 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with DCM (2 x 20 mL). The filtrate was dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain crude 3-(methylsulfonyl)propanal (7.4 g, 94 % yield) as a sticky liquid. This material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 3.39 (t, J = 6.8 Hz, 2H), 3.13 (t, J = 6.8 Hz, 2H), 2.99 (s, 3H).

Step 2. (±)-6-Benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol

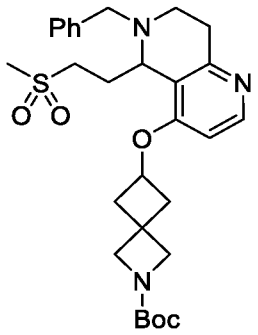


This compound was synthesized following the procedure described for the synthesis of Example 266**,** step 1, starting with 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 2 equivalents of 3-(methylsulfonyl)propanal was used. The reaction was stirred at 100 °C. After completion, saturated $NaHCO_3$ solution was added to the reaction and the mixture was extracted with DCM. The combined organic layer was washed with brine solution, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain (±)-6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol.

Yield: 14.47%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.30 (br s, 1H), 7.54 (br dd, J = 3.9, 6.4 Hz, 1H), 7.40 - 7.21 (m, 5H), 5.98 (d, J = 7.2 Hz, 1H), 3.72 - 3.52 (m, 3H), 3.24 - 3.15 (m, 1H), 3.13 - 2.96 (m, 2H), 2.92 (s, 3H), 2.84 - 2.70 (m, 2H), 2.36 - 2.24 (m, 1H), 2.19 - 2.11

(m, 1H), 1.90 - 1.76 (m, 1H); LCMS (Method G): Rt = 1.87 min, m/z = 347.1 $[M+H]^+$, 98.89%.

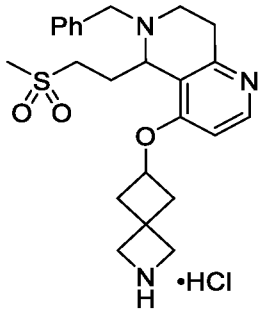
Step 3. (±)-tert-Butyl 6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 2 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol and 2.5 equivalents of K_2CO_3 were used. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 12% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate.

Yield: 60.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 5.7 Hz, 1H), 7.40 - 7.23 (m, 5H), 6.71 (d, J = 5.7 Hz, 1H), 4.75 (quin, J = 6.5 Hz, 1H), 3.96 - 3.76 (m, 5H), 3.72 - 3.54 (m, 2H), 3.29 - 3.05 (m, 3H), 2.93 (s, 3H), 2.84 - 2.77 (m, 1H), 2.73 - 2.67 (m, 2H), 2.29 - 2.05 (m, 3H), 2.01 - 1.89 (m, 1H), 1.37 (s, 9H), two peaks merged with solvent peaks; LCMS (Method G): Rt = 2.00 min, m/z = 542.2 $[M+H]^+$, 90.01%.

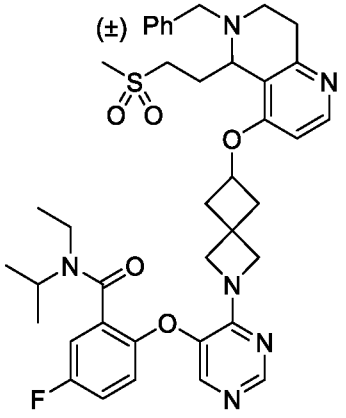
Step 4. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with (±)-*tert*-butyl 6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. After completion, the reaction was concentrated under reduced pressure. The residue was triturated with EtOAc and the supernatant was decanted. The solid was dried under reduced pressure to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride. This material was used without further purification.

Yield: 79%; LCMS (Method G): Rt = 1.38 min, m/z = 442.2 $[M+H]^+$, 72.33%.

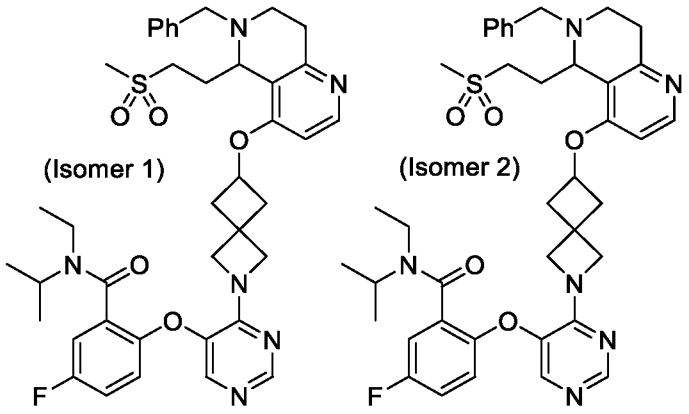
Step 5. (±)-2-((4-(6-((6-Benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine

hydrochloride was used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 8% MeOH in DCM) to obtain (±)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.
Yield: 46.5%; LCMS (Method G): Rt = 1.93 min, m/z = 743.1 $[M+H]^+$, 99.36%; Chiral SFC (Method AH): Peak 1: Rt = 7.68 min, 49.44%; Peak 2: 9.90 min, 49.25%.

Step 6. (E1)-2-((4-(6-((6-Benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

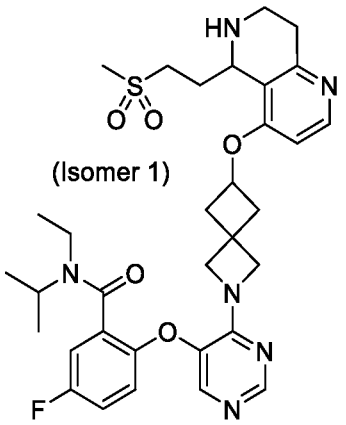


(±)-2-((4-(6-((6-Benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (350 mg) was purified by chiral Prep SFC (Method C) to obtain both isomers, (*E1*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (130 mg, 37.14% yield) and (*E2*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (140 mg, 40.0% yield) as solids.

Isomer 1. LCMS (Method G): Rt = 1.92 min, m/z = 743.1 $[M+H]^+$; HPLC (Method A): Rt = 6.02 min, 99.37%; Chiral SFC (Method AH): Rt = 7.92 min, 99.56%.

Isomer 2. LCMS (Method G): Rt = 1.93 min, m/z = 743.1 $[M+H]^+$; HPLC (Method A): Rt = 6.02 min, 99.69%; Chiral SFC (Method AH): Rt = 10.31 min, 99.78%.

Step 7. (E1)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

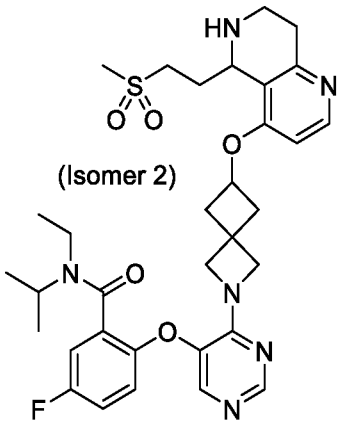


This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (*E1*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.9 equivalent of Pd-C was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 70.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.19 (d, J = 5.7 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.34 - 7.21 (m, 2H), 7.10 - 6.99 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.84 - 4.71 (m, 1H), 4.33 - 4.06 (m, 4H), 4.03 - 3.94 (m, 1H), 3.75 (spt, J = 6.5, 1H), 3.46 - 3.37 (m, 1H), 3.28 - 3.19 (m, 3H), 2.97 (s, 3H), 2.94 - 2.89 (m, 1H), 2.83 – 2.54 (m, 6H), 2.33 - 2.24 (m, 2H), 2.16 - 2.06 (m, 1H), 2.02 - 1.86 (m, 1H), 1.30 - 0.95 (m, 9H); LCMS (Method

G): Rt = 1.83 min, m/z = 653.3 $[M+H]^+$; HPLC (Method A): Rt = 4.63 min, 99.03%; Chiral SFC (Method AH): Rt = 5.59 min, 100%.

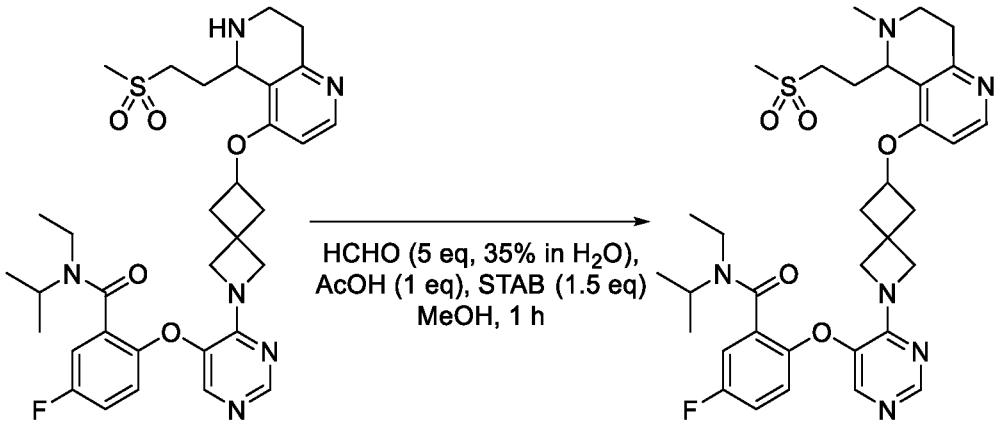
Step 8. (E2)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (*E2*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.9 equivalent of Pd-C was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 76%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.19 (d, J = 5.7 Hz, 1H), 7.80 - 7.64 (m, 1H), 7.34 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.84 - 4.72 (m, 1H), 4.35 - 4.07 (m, 4H), 4.03 - 3.94 (m, 1H), 3.75 (spt, J = 6.7, 1H), 3.45 - 3.37 (m, 1H), 3.27 - 3.19 (m, 3H), 2.97 (s, 3H), 2.95 - 2.88 (m, 1H), 2.86 - 2.56 (m, 6H), 2.32 - 2.23 (m, 2H), 2.18 - 2.04 (m, 1H), 2.03 - 1.89 (m, 1H), 1.23 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.83 min, m/z = 653.3 $[M+H]^+$; HPLC (Method A): Rt = 4.64 min, 99.86%; Chiral SFC (Method AH): Rt = 5.66 min, 100%.

Example 392. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 403)

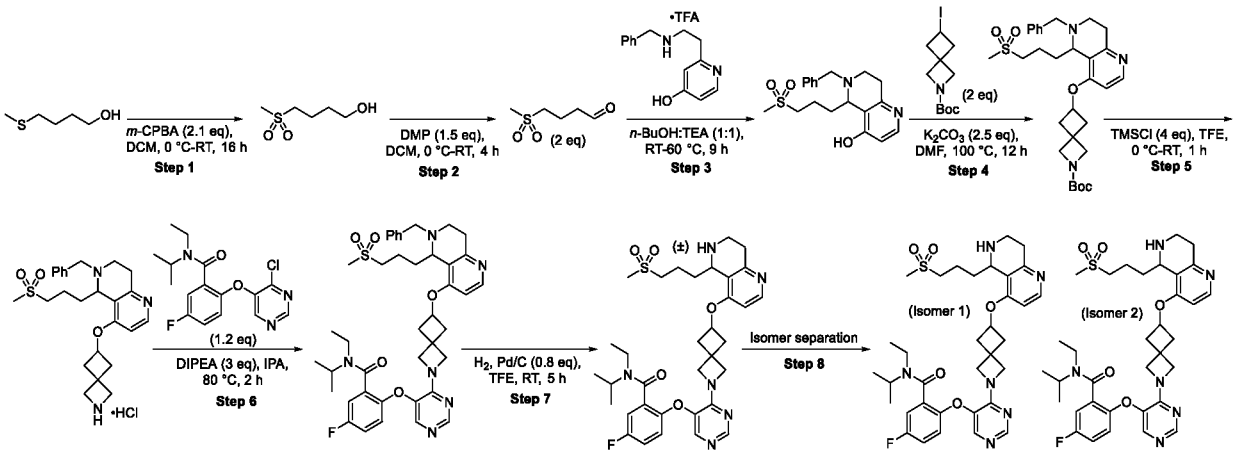


This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 1.5 equivalents of STAB was used, and MeOH was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5-(2-(methylsulfonyl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.
Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.21 (d, J = 5.6 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.71 (br d, J = 5.3 Hz, 1H), 4.83 - 4.73 (m, 1H), 4.31 - 4.07 (m, 4H), 3.80 - 3.68 (m, 2H), 3.44 - 3.35 (m, 1H), 3.28 - 3.02 (m, 4H), 2.96 (s, 3H), 2.93 - 2.69 (m, 4H), 2.34 (s, 3H), 2.32 - 2.22 (m, 2H), 2.17 - 2.04 (m, 1H), 2.01 - 1.89 (m, 1H), 1.23 - 0.99 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.68 min, m/z = 667.3 $[M+H]^+$; HPLC (Method G): Rt = 4.83 min, 99.90%; Chiral SFC (Method AH): Rt = 5.76 min, 100%.

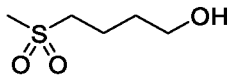
Example 393. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 404)

Example 394. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

(Compound No. 405)

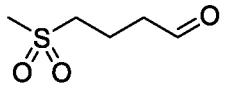


Step 1. 4-(Methylsulfonyl)butan-1-ol



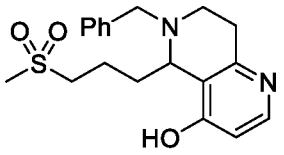
To a stirred solution of 4-(methylthio)butan-1-ol (5.0 g, 41.6 mmol) in DCM (100 mL), *m*-CPBA (15.07 g, 87 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with DCM (2 x 50 mL). The filtrate was concentrated under reduced pressure. MTBE (100 mL) was added to the residue and the mixture was washed with water (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain 4-(methylsulfonyl)butan-1-ol (5.5 g, 87% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.48 (t, J = 5.1 Hz, 1H), 3.46 - 3.39 (m, 2H), 3.16 - 3.06 (m, 2H), 2.94 (s, 3H), 1.79 - 1.65 (m, 2H), 1.58 - 1.46 (m, 2H). This material was used without further purification.

Step 2. 4-(Methylsulfonyl)butanal



In a dried, 100 mL two neck round bottom flask under a nitrogen atmosphere, 4-(methylsulfonyl)butan-1-ol (4.5 g, 29.6 mmol) was dissolved in DCM (10 mL). To this solution, Dess-Martin periodinane (18.81 g, 44.3 mmol) was added at 0 °C, and the reaction was stirred at RT for 4 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with DCM (2 x 50 mL). The filtrate was washed with saturated $NaHCO_3$ (2 x 30 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude 4-(methylsulfonyl)butanal (2.3 g, 51.8% yield) as a liquid. This material was used without further purification.

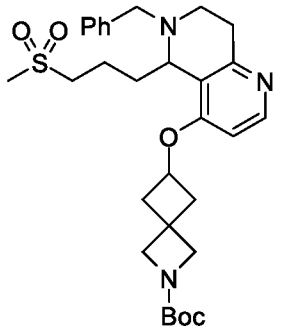
Step 3. (±)-6-Benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 2, starting with 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 2 equivalents of 4-(methylsulfonyl)butanal was used, and 1:1 TEA/*n*-BuOH was used as the solvent. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 20% MeOH in DCM) to obtain (±)-6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol as a solid.

Yield: 38.4%; LCMS (Method G): Rt = 1.70 min, m/z = 361.2 $[M+H]^+$, 78.93%.

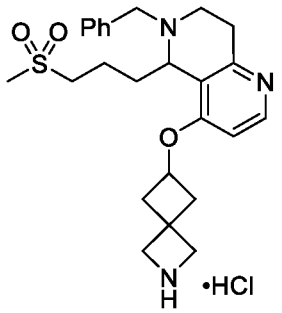
Step 4. (±)-tert-Butyl 6-((6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 2 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol and 2.5 equivalents of K_2CO_3 were used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*tert*-butyl 6-((6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a solid.

Yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, J = 5.6 Hz, 1H), 7.38 - 7.24 (m, 5H), 6.68 (d, J = 5.6 Hz, 1H), 4.71 (quin, J = 6.5 Hz, 1H), 3.97 - 3.77 (m, 4H), 3.74 - 3.63 (m, 2H), 3.60 - 3.51 (m, 1H), 3.27 - 3.14 (m, 1H), 3.12 - 2.96 (m, 3H), 2.93 (s, 3H), 2.88 - 2.80 (m, 1H), 2.77 - 2.64 (m, 2H), 2.48 - 2.45 (m, 1H), 2.22 (dd, J = 6.4, 11.7 Hz, 1H), 2.12 (dd, J = 6.4, 11.8 Hz, 1H), 1.97 - 1.73 (m, 2H), 1.72 - 1.63 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 1.96 min, m/z = 556.2 $[M+H]^+$, 99.42%.

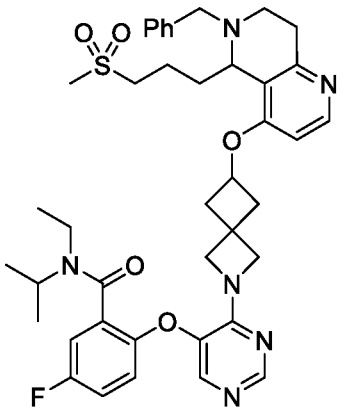
Step 5. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with 1 equivalent of (±)-*tert*-butyl 6-((6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. The reaction was concentrated under reduced pressure to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (800 mg, 91% yield), as a solid. This material was used without further purification.

Yield: 91%; LCMS (Method G): Rt = 1.47 min, m/z = 456.2 $[M+H]^+$, 91.59%.

Step 6. (±)-2-((4-(6-((6-Benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

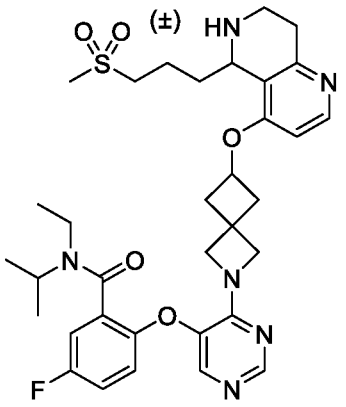


This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1.2 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-4-((2-azaspiro[3.3]heptan-6-yl)ox)-6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride and 3 equivalents of DIPEA were used. The crude compound was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 10% MeOH in DCM) to afford (±)-2-((4-(6-((6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 54.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.79 - 7.63 (m, 1H), 7.36 - 7.20 (m, 7H), 7.11 - 7.00 (m, 1H), 6.71 (br d, J = 5.6 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.32 - 4.04 (m, 4H), 3.81 - 3.65 (m, 3H), 3.60 - 3.53 (m, 1H), 3.44 -

3.36 (m, 1H), 3.28 - 3.11 (m, 2H), 3.10 - 2.95 (m, 3H), 2.92 (s, 3H), 2.87 - 2.65 (m, 3H), 2.48 - 2.43 (m, 1H), 2.32 - 2.12 (m, 2H), 1.91 - 1.77 (m, 2H), 1.74 - 1.64 (m, 2H), 1.24 - 0.93 (m, 9H); LCMS (Method G): Rt = 2.02 min, m/z = 757.4 $[M+H]^+$, 97.45%.

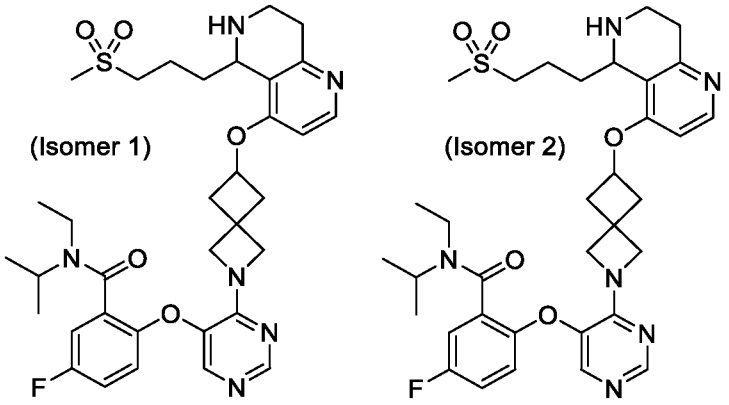
Step 7. (±)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with 1 equivalent of (±)-2-((4-(6-((6-benzyl-5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.8 equivalent of Pd-C was used. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (±)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 85%; LCMS (Method G): Rt = 1.52 min, m/z = 667.2 $[M+H]^+$, 94.31%.

Step 8. (E1)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and

(E2)-N-ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



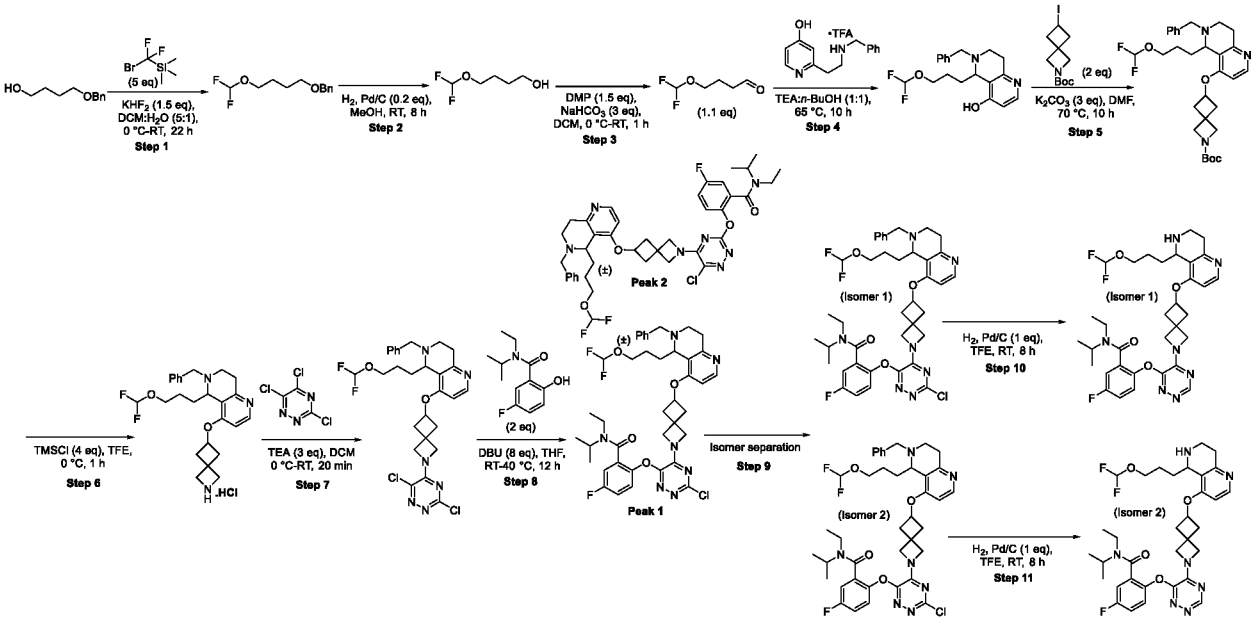
(±)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (400 mg) was purified by chiral Prep SFC (Method AL) to obtain both isomers, (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (143.98 mg, 35.99% yield) and (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(3-(methylsulfonyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (97.12 mg, 24.28% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.18 - 8.13 (m, 1H), 7.79 - 7.62 (m, 1H), 7.34 - 7.19 (m, 2H), 7.12 - 6.99 (m, 1H), 6.71 - 6.61 (m, 1H), 4.81 - 4.69 (m, 1H), 4.34 - 4.07 (m, 4H), 3.87 (br dd, J = 3.0, 9.1 Hz, 1H), 3.75 (spt, J = 6.5, 1H), 3.46 - 3.37 (m, 1H), 3.01 (br s, 4H), 2.96 (s, 3H), 2.93 - 2.87 (m, 1H), 2.86 - 2.71 (m, 2H), 2.71 - 2.61 (m, 3H), 2.32 - 2.18 (m, 2H), 2.02 - 1.58 (m, 4H), 1.26 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.59 min, m/z = 667.3 $[M+H]^+$; HPLC (Method G): Rt = 4.53 min, 99.40%; Chiral SFC (Method AAS): Rt = 4.25 min, 99.06%.

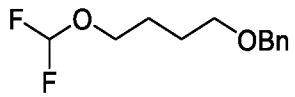
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.20 - 8.12 (m, 1H), 7.78 - 7.64 (m, 1H), 7.35 - 7.20 (m, 2H), 7.12 - 6.99 (m, 1H), 6.69 - 6.63 (m, 1H), 4.80 - 4.66 (m, 1H), 4.36 - 4.04 (m, 4H), 3.86 (dd, J = 2.9, 9.1 Hz, 1H), 3.75 (spt, J = 6.6 Hz, 1H), 3.46 - 3.37 (m, 1H), 3.29 - 2.99 (m, 4H), 2.96 (s, 3H), 2.94 - 2.89 (m, 1H), 2.86 - 2.71 (m, 2H), 2.71 - 2.57 (m, 3H), 2.32 - 2.20 (m, 2H), 2.00 - 1.60 (m, 4H), 1.29 - 0.95 (m, 9H); LCMS (Method G): Rt = 1.59 min, m/z = 667.3 $[M+H]^+$; HPLC (Method G): Rt = 4.53 min, 99.39%; Chiral SFC (Method AAS): Rt = 5.53 min, 98.66%.

Example 395. (*E1*)-2-((5-(6-((5-(3-(Difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 406)

Example 396. (*E2*)-2-((5-(6-((5-(3-(Difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 407)



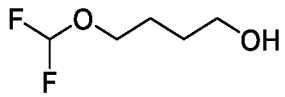
Step 1. ((4-(Difluoromethoxy)butoxy)methyl)benzene



In a 250 mL two neck round bottom flask under a nitrogen atmosphere, 4-(benzyloxy)butan-1-ol (10 g, 55.5 mmol) was dissolved in DCM (100 mL). To this solution, KHF_2 (6.50 g, 83 mmol, in 20 mL water) and (bromodifluoromethyl)trimethylsilane (22.54 g, 111 mmol) were added at RT. The reaction was stirred at RT for 1.5 h. Another 3 equivalents of (bromodifluoromethyl)trimethylsilane (33.81 g, 166.5 mmol) was added portion-wise (3 x 0.66 equivalent) to the reaction at 1.5 h time intervals at the same temperature. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (20% EtOAc in

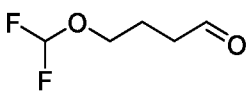
hexane). After completion, water (100 mL) was added to the reaction, and the mixture was extracted with DCM (2 x 100 mL). The combined organic layer was washed with water (2 x 30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to obtain crude ((4-(difluoromethoxy)butoxy)methyl)benzene (12 g, 94% yield). This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 - 7.24 (m, 5H), 6.85 - 6.40 (m, 1H), 4.45 (s, 2H), 3.83 (t, J = 6.2 Hz, 2H), 3.45 (t, J = 6.1 Hz, 2H), 1.72 - 1.55 (m, 4H).

Step 2. 4-(Difluoromethoxy)butan-1-ol



In a 250 mL round bottom flask, ((4-(difluoromethoxy)butoxy)methyl)benzene (6.5 g, 28.2 mmol) was added in MeOH (50 mL). To this solution, Pd-C (6.01 g, 5.65 mmol) was added at RT and the reaction was stirred under a hydrogen atmosphere (balloon pressure) at the same temperature for 18 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure to obtain the crude 4-(difluoromethoxy)butan-1-ol (3.9 g, quantitative yield). This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.86 - 6.39 (m, 1H), 4.43 (t, J = 5.2 Hz, 1H), 3.82 (t, J = 6.6 Hz, 2H), 3.46 - 3.35 (m, 2H), 1.67 - 1.55 (m, 2H), 1.52 - 1.40 (m, 2H).

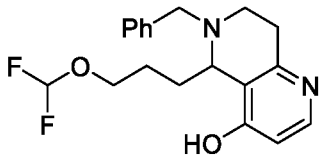
Step 3. 4-(Difluoromethoxy)butanal



In a dried, 250 mL two neck round bottom flask under a nitrogen atmosphere, 4-(difluoromethoxy)butan-1-ol (1.9 g, 13.56 mmol) was dissolved in DCM (80 mL). To this solution, sodium bicarbonate (3.42 g, 40.7 mmol) and Dess-Martin periodinane (8.63 g, 20.34 mmol) were added at 0 °C. The reaction was stirred at 0 °C for 10 min and at RT for 1 h. The

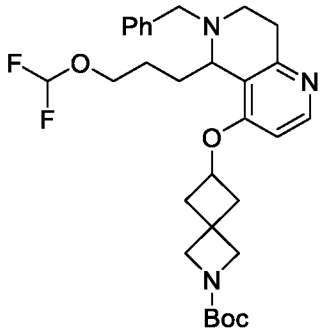
reaction progress was monitored by TLC (30% EtOAc in hexane). The reaction was concentrated under reduced pressure and pentane (100 mL) was added to the residue. The mixture was stirred for 15 min then was filtered, and the filtrate was concentrated to obtain crude 4-(difluoromethoxy)butanal (1.8 g, 96% yield) as a liquid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (t, J = 1.3 Hz, 1H), 6.86 - 6.41 (m, 1H), 3.83 (t, J = 6.6 Hz, 2H), 2.56 - 2.52 (m, 2H), 1.84 (quin, J = 6.8 Hz, 2H).

Step 4. (±)-6-Benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 2, starting with 1 equivalent of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 1.1 equivalents of 4-(difluoromethoxy)butanal was used, and 1:1 TEA/*n*-BuOH was used as the solvents. The reaction was stirred at 65 °C. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 12% MeOH in DCM) to afford (±)-6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.3 g, 31.8% yield) as a gummy solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.20 (br d, J = 3.8 Hz, 1H), 7.55 - 7.48 (m, 1H), 7.36 - 7.21 (m, 5H), 6.84 - 6.34 (m, 1H), 5.94 (d, J = 6.8 Hz, 1H), 3.81 - 3.71 (m, 2H), 3.71 - 3.63 (m, 1H), 3.53 (d, J = 13.4 Hz, 1H), 3.49 - 3.41 (m, 1H), 3.15 - 3.07 (m, 1H), 2.84 - 2.70 (m, 2H), 2.58 - 2.54 (m, 1H), 1.85 - 1.63 (m, 2H), 1.61 - 1.35 (m, 2H); LCMS (Method G): Rt = 1.62 min, m/z = 349.0 $[M+H]^+$, 99.48%.

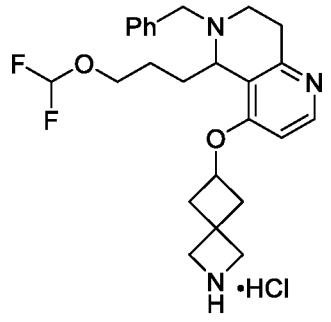
Step 5. (±)-tert-Butyl 6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



Step 5 was performed following the same procedure in two batches.

This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 2 equivalents *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used. The reaction was stirred at 70 °C. After completion, the reaction mixtures from both batches were combined for work up and purification. The reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 6% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a gummy solid.
Combined yield: 84%; LCMS (Method G): Rt = 2.36 min, m/z = 544.2 $[M+H]^+$, 94.11%.

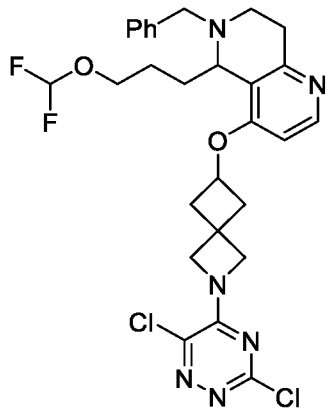
Step 6. (±)-4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with (±)-*tert*-butyl 6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc. The supernatant was decanted and the resulting residue was dried under reduced pressure to obtain crude (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride as a solid. This material was used without further purification.

Yield: Quantitative; LCMS (Method G): Rt = 1.63 min, m/z = 444.2 $[M+H]^+$, 93.50%.

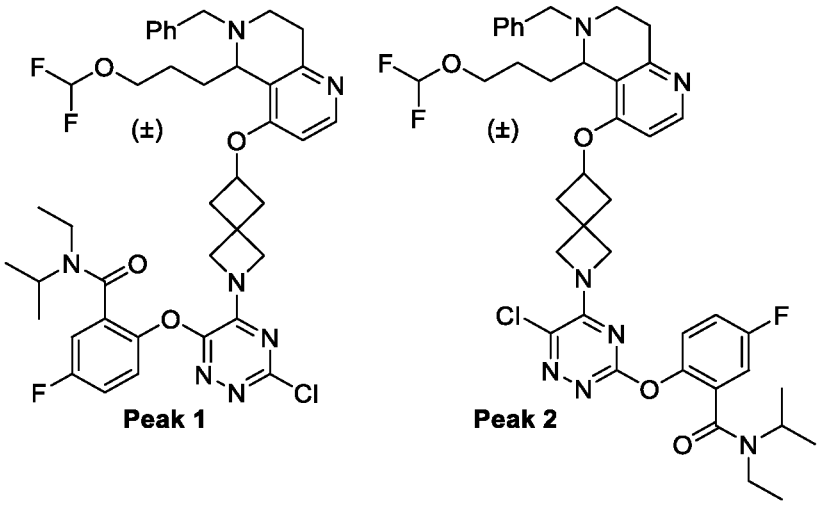
Step 7. (±)-6-Benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine



In a dried, 100 mL round bottom flask under a nitrogen atmosphere, (±)-4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (1.65 g, 3.44 mmol) was added in DCM (20 mL). To this solution, TEA (1.437 mL, 10.31 mmol) and 3,5,6-trichloro-1,2,4-triazine (0.634 g, 3.44 mmol) were added at 0 °C, and the reaction was stirred at RT for 20 min. The reaction progress was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with water (30 mL) and the mixture was extracted with DCM (3 x 20 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 7% MeOH in DCM) to obtain (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-

(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (1.3 g, 57.4% yield) as a solid. LCMS (Method G): Rt = 2.24 min, m/z = 591.1 $[M+H]^+$, 89.83%.

Step 8. (±)-2-((5-(6-((6-Benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



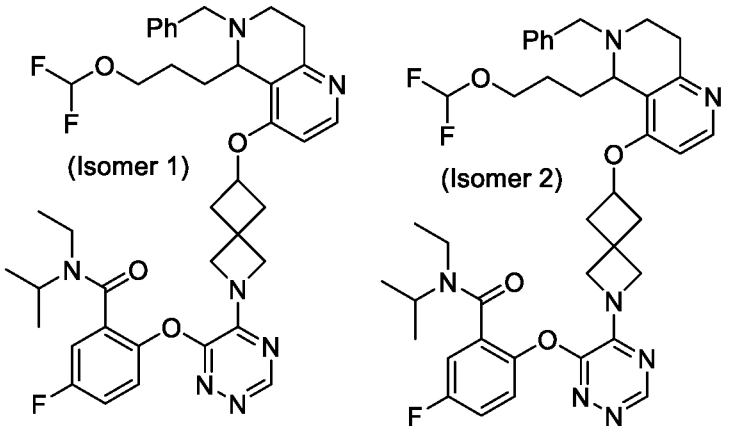
Step 8 was performed following the same procedure in three batches.

This compound was synthesized following the procedure described for the synthesis of Example 5, step 1, starting with 2 equivalents of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide, except that 1 equivalent of (±)-6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridine and 8 equivalents of DBU were used. After completion, water was added to the reaction, and the mixture was extracted with EtOAc. The combined organic layer was concentrated under reduced pressure. The crude materials from three batches were combined and purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 80% EtOAc in hexane) to obtain peak-1, (±)-2-((5-(6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Combined yield: 27.6%; LCMS (Method G): Rt = 2.36 min, m/z = 780.2 $[M+H]^+$; HPLC (Method G): Rt = 7.56 min, 95.74%; Chiral SFC (Method AAJ): Peak 1: Rt = 7.20 min, 48.57%; Peak 2: 7.86 min, 47.91%.

Note: Peak 2 was not isolated.

Step 9. (E1)-2-((5-(6-((6-Benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((5-(6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

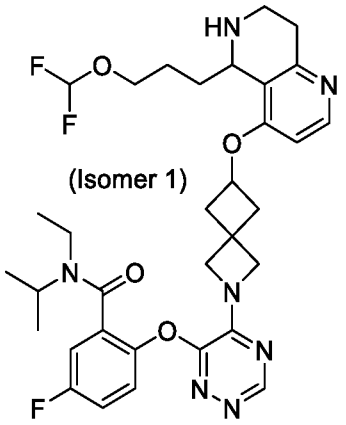


(±)-2-((5-(6-((6-Benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (350 mg) was purified by chiral Prep SFC (Method AK) to obtain both isomers, (*E1*)-2-((5-(6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (140 mg, 40% yield), and (*E2*)-2-((5-(6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (130 mg, 37.14% yield) as solids.

Peak-1. LCMS (Method G): Rt = 2.42 min, m/z = 780.2 $[M+H]^+$; HPLC (Method G): Rt = 7.58 min, 99.57%; Chiral SFC (Method AAJ): Rt = 7.35 min, 100%.

Peak-2. LCMS (Method G): Rt = 2.43 min, m/z = 780.2 $[M+H]^+$; HPLC (Method G): Rt = 7.57 min, 97.92%; Chiral SFC (Method AAJ): Rt = 7.98 min, 92.56%.

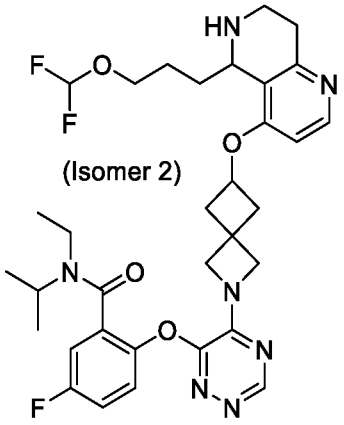
Step 10. (E1)-2-((5-(6-((5-(3-(Difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (*E1*)-2-((5-(6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of Pd-C was used. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E1*)-2-((5-(6-((5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 39.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.49 - 7.30 (m, 3H), 6.93 - 6.41 (m, 2H), 4.79 (quin, J = 6.6 Hz, 1H), 4.68 - 4.46 (m, 2H), 4.33 - 4.10 (m, 2H), 3.98 - 3.79 (m, 3H), 3.69 - 3.53 (m, 1H), 3.49 - 3.37 (m, 1H), 2.83 (br s, 6H), 2.72 - 2.64 (m, 2H), 2.35 - 2.20 (m, 2H), 1.88 - 1.49 (m, 4H), 1.19 – 0.69 (m, 9H); LCMS (Method G): Rt = 1.77 min, m/z = 656.3 $[M+H]^+$; HPLC (Method G): Rt = 5.14 min, 99.18%; Chiral SFC (Method AAV): Rt = 5.66 min, 100%.

Step 11. (E2)-2-((5-(6-((5-(3-(Difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

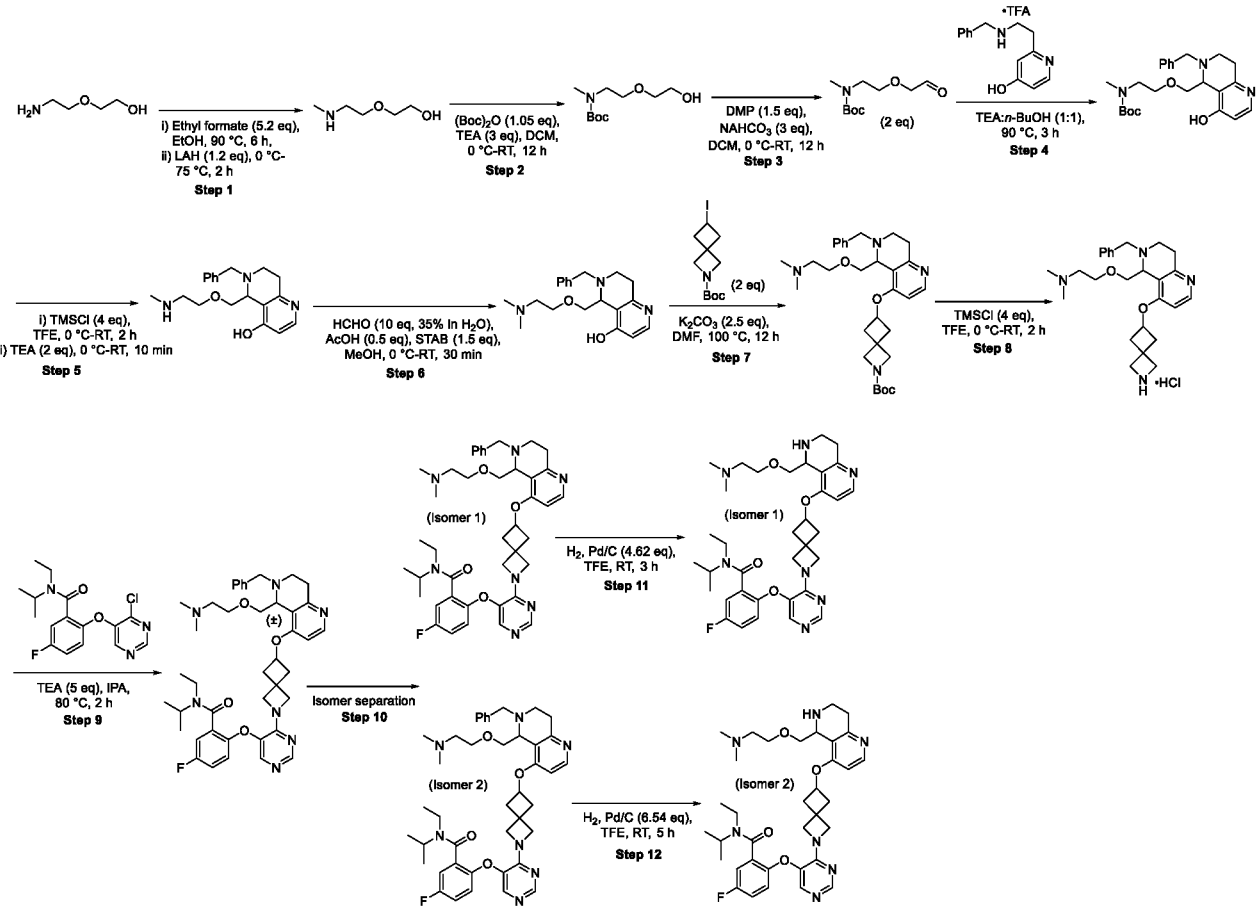


This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (*E2*)-2-((5-(6-((6-benzyl-5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of Pd-C was used. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E2*)-2-((5-(6-((5-(3-(difluoromethoxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

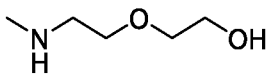
Yield: 39.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.49 - 7.28 (m, 3H), 6.88 - 6.41 (m, 2H), 4.78 (quin, J = 6.5 Hz, 1H), 4.68 - 4.46 (m, 2H), 4.32 - 4.11 (m, 2H), 3.96 - 3.79 (m, 3H), 3.69 - 3.55 (m, 1H), 3.48 - 3.37 (m, 1H), 3.18 - 2.75 (m, 6H), 2.70 - 2.62 (m, 2H), 2.35 - 2.22 (m, 2H), 1.87 - 1.52 (m, 4H), 1.19 - 0.61 (m, 9H); LCMS (Method G): Rt = 1.77 min, m/z = 656.3 $[M+H]^+$; HPLC (Method G): Rt = 5.13 min, 99.10%; Chiral SFC (Method AAV): Rt = 5.94 min, 100%.

Example 397. (*E1*)-2-((4-(6-((5-((2-(Dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 408)

Example 398. (*E2*)-2-((4-(6-((5-((2-(Dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 409)



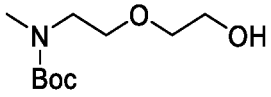
Step 1. 2-(2-(Methylamino)ethoxy)ethan-1-ol



This compound was synthesized following the procedure described for the synthesis of Intermediate 46, step 1, starting with 1 equivalent of 2-(2-aminoethoxy)ethan-1-ol, except that 5.2 equivalents of ethyl formate was used, and the reaction was stirred at 90 °C, to obtain *N*-(2-(2-hydroxyethoxy)ethyl)formamide. In the next step, 1.2 equivalents of LAH was used and the reaction was stirred at 75 °C, to obtain 2-(2-(methylamino)ethoxy)ethan-1-ol as a liquid.

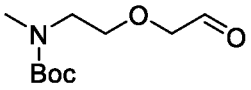
Yield: 98%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.51 - 3.43 (m, 4H), 3.42 - 3.38 (m, 2H), 2.59 (t, J = 5.7 Hz, 2H), 2.28 (s, 3H), two protons merged with solvent peaks. This material was used without further purification.

Step 2. tert-Butyl (2-(2-hydroxyethoxy)ethyl)(methyl)carbamate



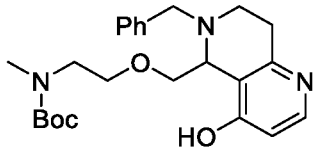
This compound was synthesized following the procedure described for the synthesis of Intermediate 46, step 2, starting with 1 equivalent of 2-(2-(methylamino)ethoxy)ethan-1-ol, except that 1.05 equivalents of $(Boc)_2O$ was used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 60% EtOAc in hexane) to obtain *tert*-butyl (2-(2-hydroxyethoxy)ethyl)(methyl)carbamate as a solid.
Yield: 62.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.57 (br t, J = 5.1 Hz, 1H), 3.52 - 3.45 (m, 4H), 3.44 - 3.39 (m, 2H), 3.30 (t, J = 5.1 Hz, 2H), 2.87 - 2.76 (m, 3H), 1.39 (s, 9H).

Step 3. tert-Butyl methyl(2-(2-oxoethoxy)ethyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 46, step 3a, starting with 1 equivalent of *tert*-butyl (2-(2-hydroxyethoxy)ethyl)(methyl)carbamate, except that 3 equivalents of $NaHCO_3$ was used. After completion, DCM was added to the reaction, the mixture was filtered through a Celite® pad, and the pad was washed with DCM. The filtrate was concentrated under reduced pressure and the residue was taken up in hexane. The hexane layer was filtered and the filtrate was concentrated under reduced pressure to obtain crude *tert*-butyl methyl(2-(2-oxoethoxy)ethyl)carbamate as a liquid. This material was used without further purification.
Yield: 54.2%.

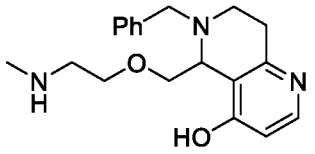
Step 4. (±)-tert-Butyl (2-((6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methoxy)ethyl)(methyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 2, starting with 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 2 equivalents of *tert*-butyl methyl(2-(2-oxoethoxy)ethyl)carbamate was used and 1:1 TEA/*n*-BuOH was used as the solvents. The reaction was stirred at 90 °C. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 6% MeOH in DCM) to obtain (±)-*tert*-butyl (2-((6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methoxy)ethyl)(methyl)carbamate.

Yield: 49.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (br s, 1H), 7.57 - 7.48 (m, 1H), 7.40 - 7.20 (m, 5H), 5.95 (br d, J = 6.7 Hz, 1H), 3.89 - 3.79 (m, 2H), 3.71 - 3.58 (m, 2H), 3.54 - 3.41 (m, 3H), 3.31 - 3.26 (m, 2H), 3.24 - 3.13 (m, 2H), 2.87 - 2.64 (m, 5H), 1.38 (s, 9H); LCMS (Method G): Rt = 1.79 min, m/z = 428.3 $[M+H]^+$, 93.13%.

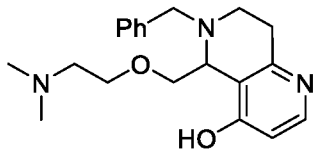
Step 5. (±)-6-Benzyl-5-((2-(methylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



In a dried, 100 mL round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl (2-((6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methoxy)ethyl)(methyl)carbamate (1.15 g, 2.69 mmol) was added in TFE (15 mL). To this solution, TMSCl (1.375 mL, 10.76 mmol) was added at 0 °C and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure and the residue was

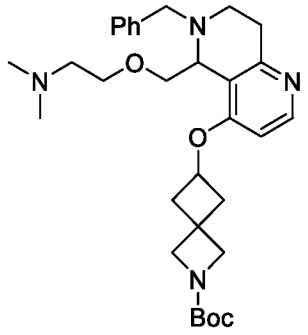
triturated with EtOAc (50 mL). The supernatant was decanted, and the resulting residue was dried under reduced pressure. The resulting hydrochloride salt was added to DCM (20 mL) and TEA (0.750 mL, 5.38 mmol) was added. The mixture was stirred at RT for 10 min and concentrated under reduced pressure to obtain crude (±)-6-benzyl-5-((2-(methylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.2 g, quantitative yield). This material was used without further purification. LCMS (Method G): Rt = 1.08 min, m/z = 328.2 $[M+H]^+$, 92.89%.

Step 6. (±)-6-Benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



In a dried, 100 mL round bottom flask under a nitrogen atmosphere, (±)-6-benzyl-5-((2-(methylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (1.2 g, 3.66 mmol) was added in MeOH (15 mL). To this solution, HCHO (1.01 mL, 36.6 mmol, 35% in H_2O) and AcOH (0.105 mL, 1.832 mmol) were added at 0 °C, and the reaction was stirred at RT for 5 min. To this reaction, STAB (1.165 g, 5.50 mmol) was added at 0 °C, and the reaction was stirred at RT for 30 min. The reaction progress was monitored by TLC (10% MeOH In DCM). After completion, the reaction was concentrated under reduced pressure, saturated $NaHCO_3$ (20 mL) was added, and the mixture was extracted with 10% MeOH in DCM (40 mL). The combined organic layer was filtered through a Celite® pad, and the pad was washed with 10% MeOH in DCM (2 x 50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by chromatography over neutral alumina, using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain (±)-6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (525 mg, 41.0% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 11.24 (br d, J = 2.8 Hz, 1H), 7.56 - 7.45 (m, 1H), 7.40 - 7.18 (m, 5H), 5.93 (d, J = 7.1 Hz, 1H), 4.12 - 3.99 (m, 2H), 3.88 - 3.76 (m, 2H), 3.72 - 3.54 (m, 2H), 3.50 - 3.39 (m, 3H), 2.81 - 2.63 (m, 2H), 2.37 (t, J = 6.0 Hz, 2H), 2.13 (s, 6H); LCMS (Method G): Rt = 1.17 min, m/z = 342.2 $[M+H]^+$, 97.80%.

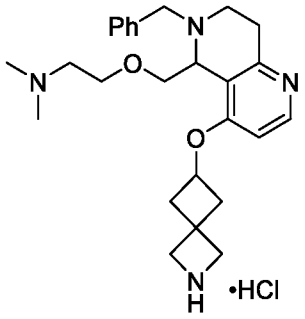
Step 7. (±)-tert-Butyl 6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



Step 7 was performed following the same procedure in two batches.

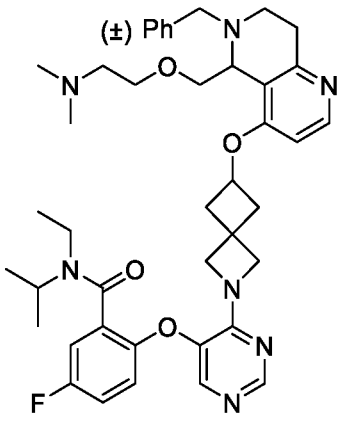
This compound was synthesized following the procedure described for the synthesis of Example 266, step 2, starting with 2 equivalents of *tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of (±)-6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol and 2.5 equivalents of K_2CO_3 were used. After completion, EtOAc was added to the reaction, the mixture was filtered through a Celite® pad, and the pad was washed with EtOAc. The organic layer was washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude from both batches was combined and purified by silica gel column chromatography using MeOH in DCM (product was eluted at 14% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a solid. Combined yield: 61.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (d, J = 5.7 Hz, 1H), 7.41 - 7.20 (m, 5H), 6.77 (br d, J = 5.7 Hz, 1H), 4.76 (quin, J = 6.5 Hz, 1H), 4.19 - 4.04 (m, 2H), 3.99 - 3.61 (m, 9H), 3.58 - 3.21 (m, 8H), 3.02 - 2.82 (m, 3H), 2.74 - 2.67 (m, 1H), 2.63 - 2.54 (m, 1H), 2.41 - 2.33 (m, 1H), 2.25 - 2.12 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 2.03 min, m/z = 537.4 $[M+H]^+$, 96.11%.

Step 8. (±)-2-((4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methoxy)-N,N-dimethylethan-1-amine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with 1 equivalent of (±)-*tert*-butyl 6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, to obtain crude (±)-2-((4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methoxy)-*N*,*N*-dimethylethan-1-amine hydrochloride as a solid. This material was used without further purification. Yield: 58.0%; LCMS (Method B): Rt = 0.21 min, m/z = 437.3 $[M+H]^+$, 42.75%.

Step 9. (±)-2-((4-(6-((6-Benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

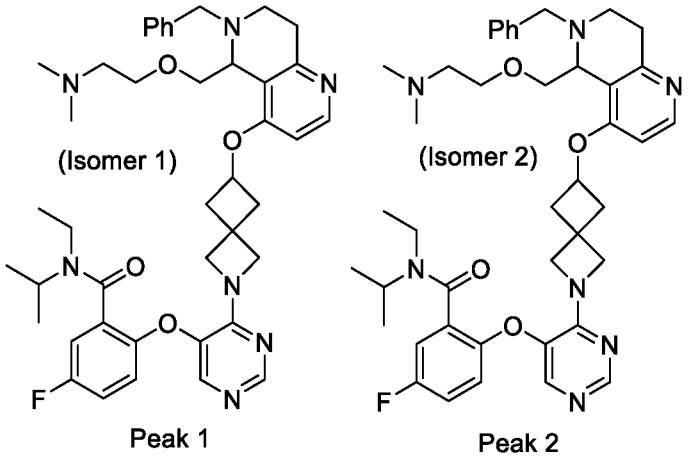


This compound was synthesized following the procedure described for the synthesis of Example 266 step 4, starting with 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-2-((4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methoxy)-*N*,*N*-dimethylethan-1-amine hydrochloride was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM

NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((4-(6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 9.1%; LCMS (Method G): Rt = 1.94 min, m/z = 738.3 $[M+H]^+$, 95.36%. Chiral SFC (Method AAT): Peak 1: Rt = 6.23 min, 49.92%; Peak 2: Rt = 7.65 min, 50.08%.

Step 10. (E1)-2-((4-(6-((6-Benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

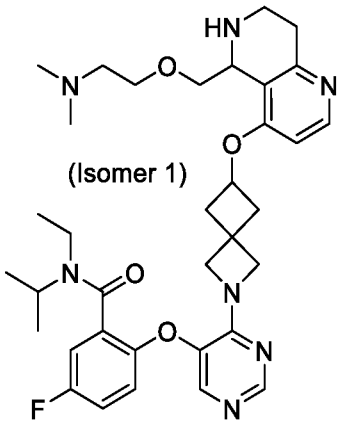


(±)-2-((4-(6-((6-Benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (140 mg) was purified by chiral Prep SFC (Method AO) to obtain both isomers, (*E1*)-2-((4-(6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (52 mg, 37.14% yield) and (*E2*)-2-((4-(6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (54 mg, 38.57% yield).

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.24 - 8.19 (m, 1H), 7.78 - 7.61 (m, 1H), 7.41 - 7.19 (m, 7H), 7.12 - 7.01 (m, 1H), 6.73 - 6.67 (m, 1H), 4.75 (quin, J = 6.6 Hz, 1H), 4.34 - 4.01 (m, 5H), 3.89 - 3.81 (m, 1H), 3.79 - 3.64 (m, 3H), 3.54 - 3.36 (m, 4H), 3.28 - 3.10 (m, 2H), 2.92 - 2.70 (m, 4H), 2.60 - 2.55 (m, 1H), 2.41 - 2.31 (m, 2H), 2.28 - 2.15 (m, 2H), 2.11 (s, 6H), 1.22 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.80 min, m/z = 738.3 $[M+H]^+$; HPLC (Method G): Rt = 5.44 min, 99.90%; Chiral SFC (Method AAT): Rt = 6.89 min, 99.58%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.22 (d, J = 5.8 Hz, 1H), 7.76 - 7.64 (m, 1H), 7.40 - 7.20 (m, 7H), 7.11 - 7.00 (m, 1H), 6.70 (d, J = 5.8 Hz, 1H), 4.80 - 4.72 (m, 1H), 4.31 - 4.03 (m, 5H), 3.88 - 3.82 (m, 1H), 3.79 - 3.65 (m, 3H), 3.55 - 3.36 (m, 4H), 3.26 - 3.19 (m, 2H), 2.97 - 2.75 (m, 4H), 2.60 - 2.55 (m, 1H), 2.40 - 2.32 (m, 2H), 2.28 - 2.16 (m, 2H), 2.11 (s, 6H), 1.22 - 0.96 (m, 9H), HPLC (Method G): Rt = 5.47 min, 96.26%; Chiral SFC (Method AAT): Rt = 8.38 min, 99.84%.

Step 11. (E1)-2-((4-(6-((5-((2-(Dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

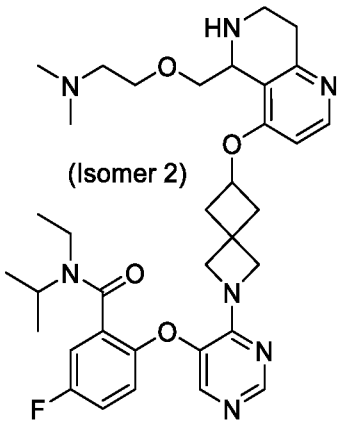


This compound was synthesized following the procedure described for the synthesis of Example 279 and 280, step 2, starting with 1 equivalent of (*E1*)-2-((4-(6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 4.62 equivalents of Pd-C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one

(Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*E1*)-2-((4-(6-((5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 22.60%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.19 (d, *J* = 5.5 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.35 - 7.22 (m, 2H), 7.13 - 7.00 (m, 1H), 6.67 (br d, *J* = 5.6 Hz, 1H), 4.83 - 4.69 (m, 1H), 4.35 - 4.05 (m, 5H), 3.75 (spt, *J* = 6.5 Hz, 1H), 3.63 - 3.43 (m, 5H), 3.24 - 3.07 (m, 3H), 2.98 - 2.58 (m, 5H), 2.42 (br t, *J* = 5.7 Hz, 2H), 2.30 - 2.19 (m, 2H), 2.16 (s, 6H), 1.22 - 0.93 (m, 9H); LCMS (Method G): Rt = 1.68 min, m/z = 648.3 $[M+H]^+$; HPLC (Method G): Rt = 4.41 min, 99.57%; Chiral SFC (Method AAT): Rt = 5.35 min, 99.04%.

Step 12. (E2)-2-((4-(6-((5-((2-(Dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

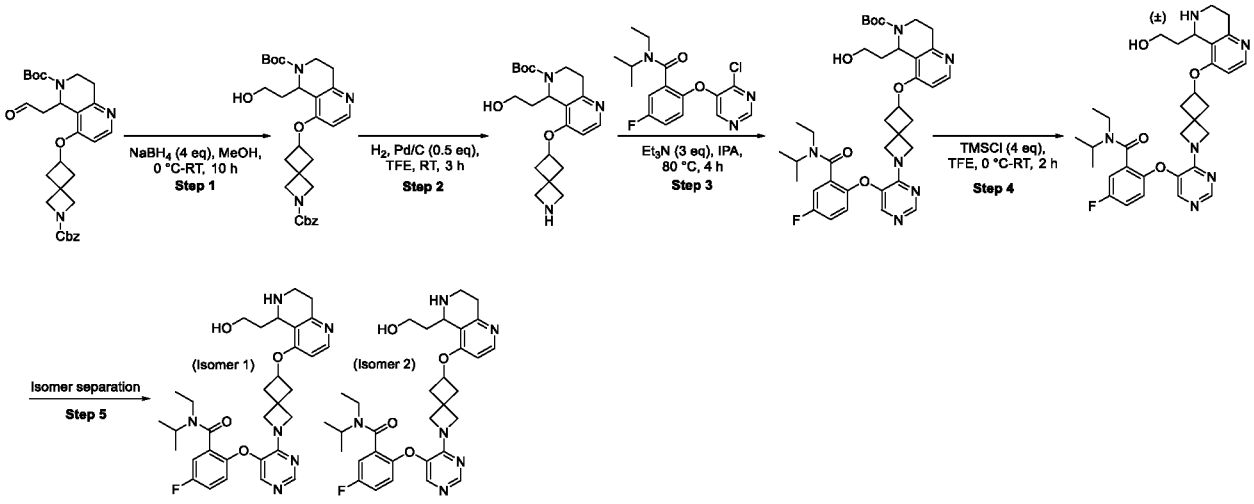


This compound was synthesized following the procedure described for the synthesis of Example 279 and 280, step 2, starting with (*E2*)-2-((4-(6-((6-benzyl-5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 6.54 equivalents of Pd-C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*E2*)-2-((4-(6-((5-((2-(dimethylamino)ethoxy)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

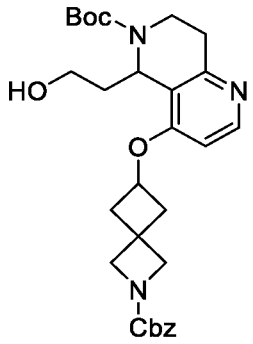
Yield: 40.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.35 - 7.22 (m, 2H), 7.12 - 7.00 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.81 - 4.70 (m, 1H), 4.33 - 4.07 (m, 5H), 3.74 (spt, J = 6.4 Hz, 1H), 3.62 - 3.44 (m, 4H), 3.43 - 3.38 (m, 1H), 3.28 - 3.21 (m, 1H), 3.17 - 3.05 (m, 2H), 2.96 - 2.60 (m, 5H), 2.40 (br t, J = 5.8 Hz, 2H), 2.30 - 2.19 (m, 2H), 2.14 (s, 6H), 1.23 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.67 min, m/z = 648.4 $[M+H]^+$; HPLC (Method G): Rt = 4.42 min, 99.62%; Chiral SFC (Method AAT): Rt = 7.94 min, 100%.

Example 399. (*E1*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 410)

Example 400. (*E2*)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (Compound No. 411)

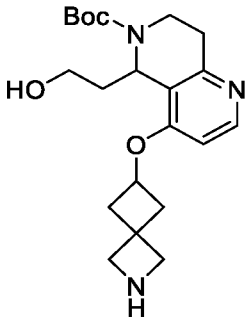


Step 1. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-oxoethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (650 mg, 1.246 mmol) in MeOH (5 mL), $NaBH_4$ (189 mg, 4.98 mmol) was added at 0 °C. The reaction was stirred at RT for 10 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. 10% $NaHCO_3$ solution (20 mL) was added to this residue, and the mixture was extracted with EtOAc (3 x 35 mL). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (405 mg, 61.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, J = 5.6 Hz, 1H), 7.43 - 7.26 (m, 5H), 6.71 (br d, J = 5.5 Hz, 1H), 5.25 - 5.10 (m, 1H), 5.03 (s, 2H), 4.85 - 4.69 (m, 1H), 4.46 - 4.31 (m, 1H), 4.18 - 3.95 (m, 4H), 3.56 - 3.37 (m, 2H), 3.20 - 3.16 (m, 2H), 2.84 - 2.72 (m, 4H), 2.34 - 2.18 (m, 2H), 2.02 - 1.72 (m, 2H), 1.41 (s, 9H); LCMS (Method G): Rt = 2.38 min, m/z = 524.3 $[M+H]^+$, 99.35%.

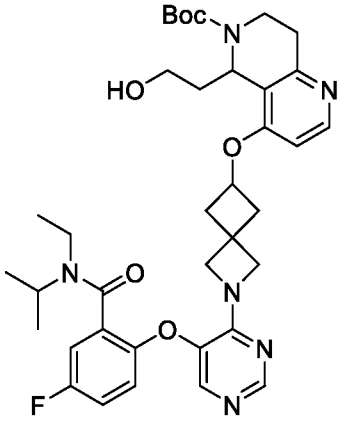
Step 2. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This reaction was performed following the same procedure in two batches (100 mg and 300 mg).

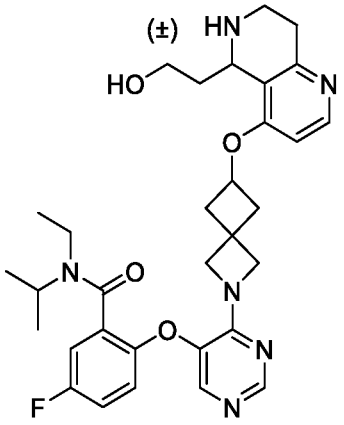
To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.191 mmol) in TFE (2 mL), Pd-C (100 mg, 0.940 mmol) was added at RT. The reaction was stirred at RT for 6 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 10 mL). The filtrate from the two batches were combined and concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (70 mg, 92% combined yield). This material was used without further purification. LCMS (Method G): Rt = 1.30 min, m/z = 390.1 $[M+H]^+$, 98.02%.

Step 3. (±)-tert-Butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and 3 equivalents of TEA were used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.
Yield: 44.8%; LCMS (Method G): Rt = 1.90 min, m/z = 691.3 $[M+H]^+$, 87.66%.

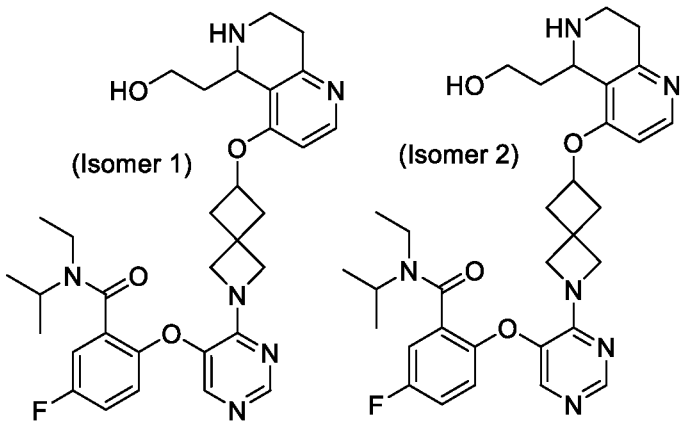
Step 4. (±)-N-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with 1 equivalent of (±)-*tert*-butyl 4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide as a solid.

Yield: 93%; LCMS (Method G): Rt = 1.70 min, m/z = 591.4 $[M+H]^+$, 95.54%. Chiral SFC (Method AZ): Peak-1: Rt = 11.91 min, 49.22%; Peak-2: Rt = 14.26 min, 46.91%.

Step 5. (E1)-N-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide and (E2)-N-ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-isopropylbenzamide



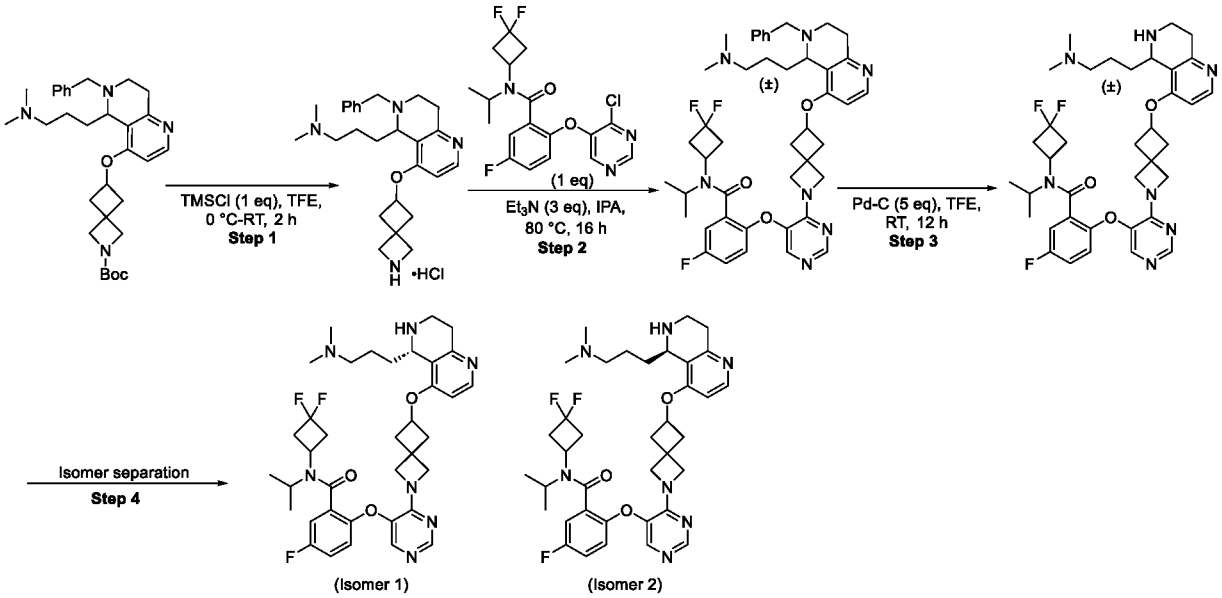
(±)-*N*-Ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (240 mg) was purified by chiral Prep SFC (Method AG) to obtain both isomers, (*E1*)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (38.39 mg, 15.99% yield) and (*E2*)-*N*-ethyl-5-fluoro-2-((4-(6-((5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-isopropylbenzamide (36.81 mg, 15.33% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.16 (br d, J = 5.6 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 - 6.98 (m, 1H), 6.64 (br d, J = 5.8 Hz, 1H), 4.96 - 4.70 (m, 2H), 4.31 - 3.98 (m, 6H), 3.81 - 3.72 (m, 1H), 3.64 – 3.56 (m, 2H), 3.19 - 3.09 (m, 1H), 3.10 - 2.98 (m, 1H), 2.97 - 2.87 (m, 1H), 2.82 - 2.63 (m, 5H), 2.29 - 2.17 (m, 2H), 1.80 - 1.65 (m, 2H), 1.31 - 0.92 (m, 9H); LCMS (Method G): Rt = 1.44 min, m/z = 591.2 $[M+H]^+$; HPLC (Method G): Rt = 4.37 min, 99.58%; Chiral SFC (Method AZ): Rt = 11.52 min, 96.78%.

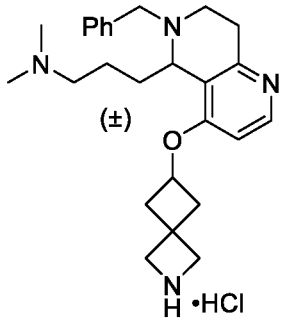
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.24 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.79 - 7.66 (m, 1H), 7.35 - 7.21 (m, 2H), 7.10 - 7.01 (m, 1H), 6.65 (br d, J = 5.4 Hz, 1H), 4.93 - 4.67 (m, 2H), 4.33 - 3.99 (m, 6H), 3.82 - 3.71 (m, 1H), 3.64 – 3.56 (m, 2H), 3.19 - 3.09 (m, 1H), 3.08 - 2.99 (m, 1H), 2.96 - 2.89 (m, 1H), 2.85 - 2.62 (m, 5H), 2.29 - 2.18 (m, 2H), 1.84 - 1.66 (m, 2H), 1.33 - 0.92 (m, 9H); LCMS (Method G): Rt = 1.45 min, m/z = 591.2 $[M+H]^+$; HPLC (Method G): Rt = 4.37 min, 99.63%; Chiral SFC (Method AZ): Rt = 13.59 min, 96.96%.

Example 401. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 316)

Example 402. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 317)

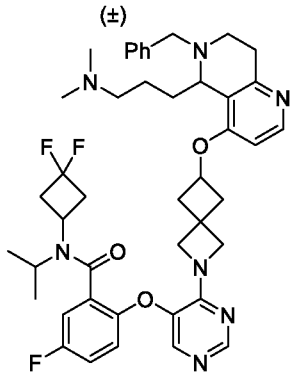


Step 1. (±)-3-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylpropan-1-amine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 266, step 3, starting with 1 equivalent of (±)-*tert*-butyl 6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of TMSCl was added slowly at 0 °C. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in DMC). After completion, the reaction was concentrated under reduced pressure, and the residue was triturated with EtOAc. The EtOAc layer was decanted, and the solid was dried under reduced pressure to obtain crude (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride (1.6 g, quantitative yield) as a solid. LCMS (Method G): Rt = 1.30 min, m/z = 421.3 $[M+H]^+$, 83.86%. This material was used without further purification.

Step 2. (±)-2-((4-(6-((6-Benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide

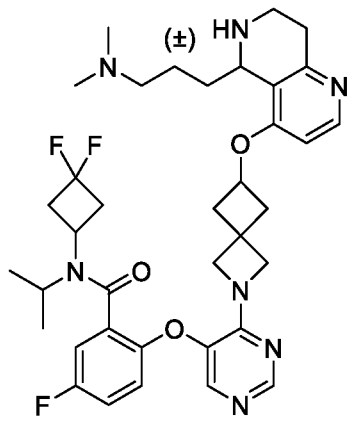


This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1 equivalent of (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-

6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride and 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of Et_3N was used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a semi-solid.

Yield: 34.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.77 (s, 1H), 7.37 - 7.29 (m, 4H), 7.28 - 7.22 (m, 2H), 7.09 - 7.04 (m, 1H), 6.68 (d, J = 5.8 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.32 - 4.05 (m, 4H), 3.96 - 3.83 (m, 1H), 3.77 - 3.65 (m, 5H), 3.523.48 (m, 1H), 3.25 - 3.19 (m, 1H), 3.17 (d, J = 5.1 Hz, 1H), 2.97 - 2.70 (m, 6H), 2.48-2.44 (m, 1H), 2.23 - 2.06 (m, 4H), 2.04 (s, 6H), 1.59 - 1.45 (m, 4H), 1.13 - 0.97 (m, 6H); LCMS (Method D): Rt = 2.13 min, m/z = 784.3 $[M+H]^+$, 95.59%.

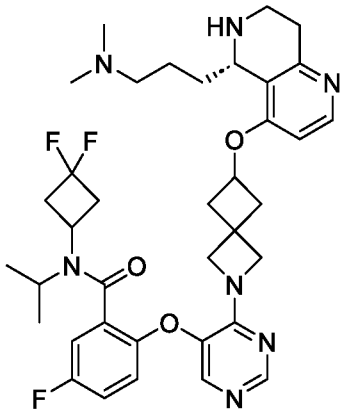
Step 3. (±)-N-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide



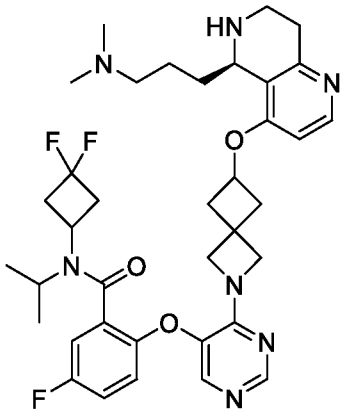
To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (300 mg, 0.383 mmol) in 2,2,2-trifluoroethanol (10 mL), Pd-C (51.6 mg, 0.048 mmol) was added at RT. The reaction was stirred under a hydrogen atmosphere (balloon pressure) at RT for 12 h. The progress of the

reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluoroethanol (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (180 mg, 0.259 mmol) as a semisolid. LCMS (Method G): Rt = 1.68 min, m/z = 694.6 $[M+H]^+$, 91.29%; Chiral SFC (Method AL): Peak 1: Rt = 2.45 min, 47.65%; Peak 2: Rt = 3.80 min, 46.01%.

Step 4. (E1)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide and (E2)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide



(Isomer 1)



(Isomer 2)

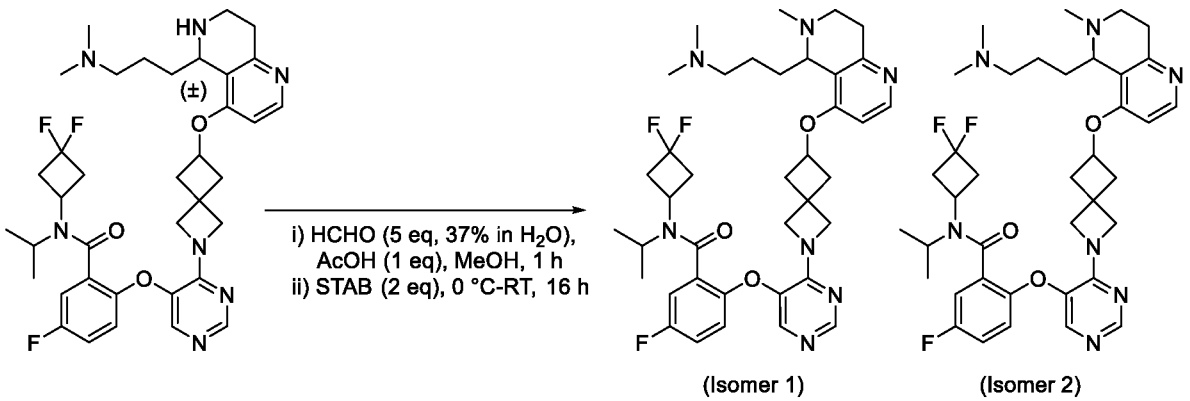
(±)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (180 mg) was purified by chiral Prep SFC (Method C) to obtain both isomers, (*E1*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (32.91 mg, 12.36% yield) and (*E2*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (48.76 mg, 18.29% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.15 (d, J = 5.7 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.33 (m, 1H), 7.31 - 7.24 (m, 1H), 7.09 - 7.03 (m, 1H), 6.63 (d, J = 5.7 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.31 - 4.08 (m, 4H), 3.96 - 3.80 (m, 2H), 3.79 - 3.66 (m, 2H), 3.61 - 3.48 (m, 1H), 3.05 - 2.96 (m, 1H), 2.94 - 2.86 (m, 1H), 2.85-2.74 (m, 3H), 2.73 - 2.60 (m, 4H), 2.28 - 2.14 (m, 4H), 2.10 (s, 6H), 1.63 - 1.44 (m, 4H), 1.10 (d, J = 5.8 Hz, 3H), 1.00 (d, J = 5.8 Hz, 3H); LCMS (Method G): Rt = 2.03 min, m/z = 694.4 $[M+H]^+$; HPLC (Method A): Rt = 4.98 min, 99.71%; Chiral SFC (Method AL): Rt = 2.24 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.78 (m, 1H), 7.38 - 7.33 (m, 1H), 7.31 - 7.24 (m, 1H), 7.09 - 7.04 (m, 1H), 6.63 (d, J = 5.7 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.33 - 4.06 (m, 4H), 3.96 - 3.80 (m, 2H), 3.78 - 3.65 (m, 2H), 3.62 - 3.47 (m, 1H), 3.06 - 2.95 (m, 1H), 2.95 - 2.87 (m, 1H), 2.84 - 2.74 (m, 3H), 2.73 - 2.60 (m, 4H), 2.28 - 2.14 (m, 4H), 2.10 (s, 6H), 1.63 - 1.43 (m, 4H), 1.10 (d, J = 5.9 Hz, 3H), 1.00 (d, J = 5.9 Hz, 3H); LCMS (Method G): Rt = 2.00 min, m/z = 694.4 $[M+H]^+$; HPLC (Method A): Rt = 4.98 min, 99.61%; Chiral SFC (Method AL): Rt = 2.74 min, 100%.

Example 403. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 326)



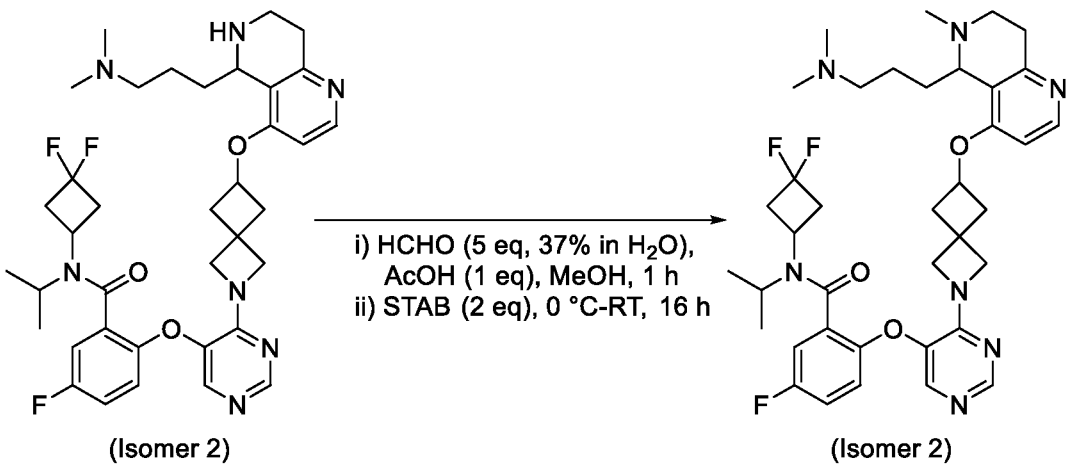
This compound was synthesized following the procedure described for the synthesis of Example 217, starting with (±)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-

(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide, except that 2 equivalents of STAB were used, and MeOH was used as a solvent. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH), then by chiral Prep SFC (Method W) to obtain (*E1*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid.

Isomer 1. Yield: 10.01%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.33 (m, 1H), 7.30 - 7.24 (m, 1H), 7.09 - 7.04 (m, 1H), 6.66 (d, J = 5.7 Hz, 1H), 4.79 - 4.69 (m, 1H), 4.33 - 4.07 (m, 4H), 3.97 - 3.84 (m, 1H), 3.79 - 3.65 (m, 2H), 3.60 - 3.49 (m, 2H), 3.19 - 3.08 (m, 1H), 2.89 - 2.77 (m, 2H), 2.77 - 2.70 (m, 4H), 2.32 (s, 3H), 2.30 - 2.22 (m, 2H), 2.22 - 2.14 (m, 3H), 2.07 (s, 6H), 1.58 - 1.46 (m, 4H), 1.10 (d, J = 5.9 Hz, 3H), 1.01 (d, J = 5.8 Hz, 3H); LCMS (Method G): Rt = 1.94 min, m/z = 708.6 $[M+H]^+$; HPLC (Method A): Rt = 5.30 min, 99.17%; Chiral SFC (Method AAD): Rt = 7.67 min, 99.86%.

Note: Only isomer 1 was isolated.

Example 404. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 331)



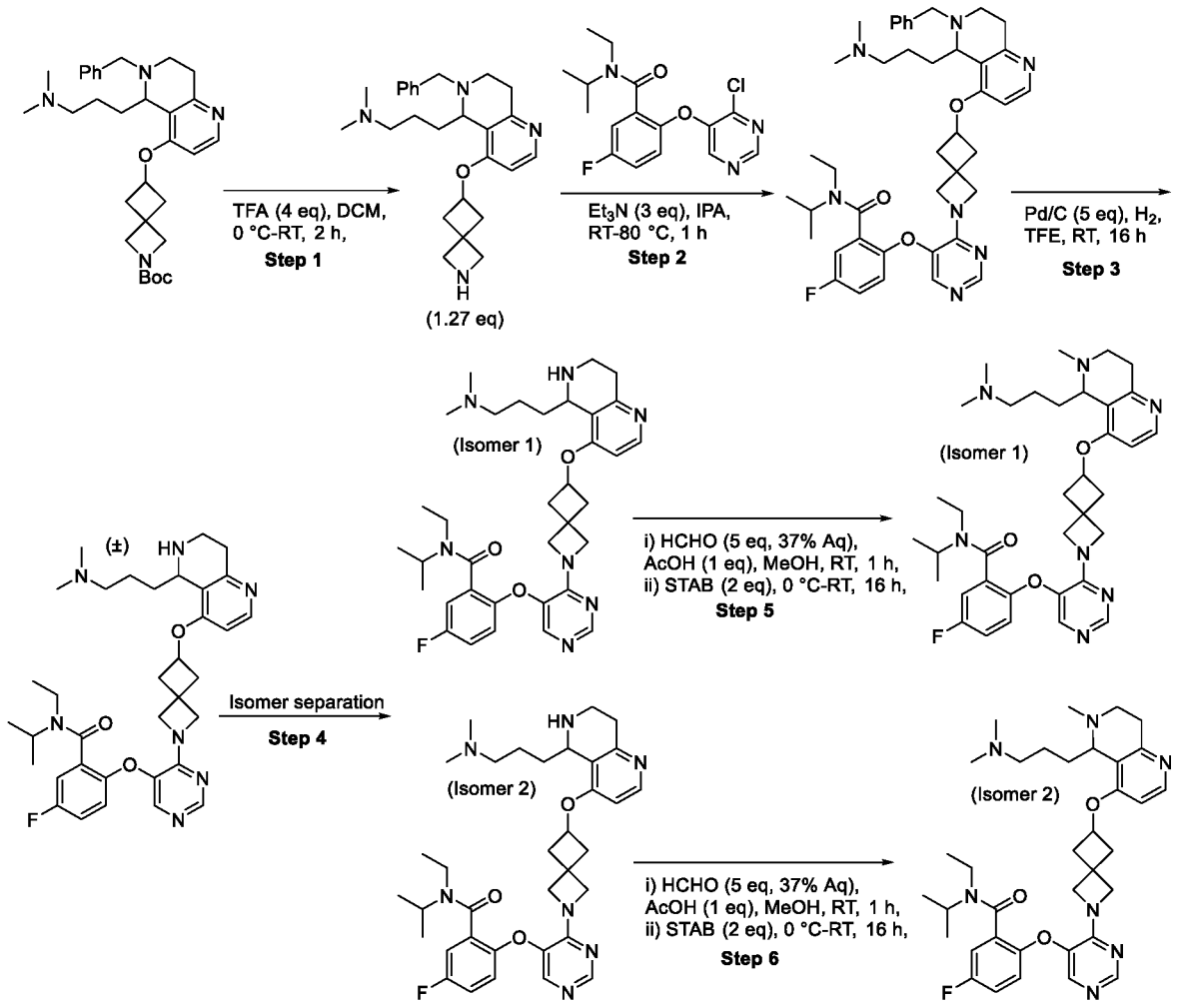
(Isomer 2) (Isomer 2)

This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of (*E2*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (*E2*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (75.14 mg, 56.2% yield) as a solid.

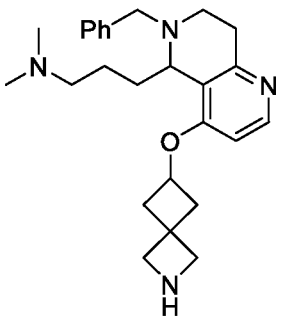
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 (s, 1H), 7.38 - 7.33 (m, 1H), 7.31 - 7.24 (m, 1H), 7.09 - 7.04 (m, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.32 - 4.07 (m, 4H), 3.96 - 3.85 (m, 1H), 3.79 - 3.65 (m, 2H), 3.61-3.49 (m, 2H), 3.19 - 3.08 (m, 1H), 2.90 - 2.77 (m, 2H), 2.77 - 2.64 (m, 4H), 2.32 (s, 3H), 2.30 - 2.21 (m, 2H), 2.20 - 2.15 (m, 3H), 2.07 (s, 6H), 1.58 - 1.46 (m, 4H), 1.10 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 5.9 Hz, 3H); LCMS (Method G): Rt = 1.89 min, m/z = 708.4 $[M+H]^+$; HPLC (Method A): Rt = 5.41 min, 99.22%; Chiral SFC (Method AAD): Rt = 10.01 min, 99.68%.

Example 405. (*E1*)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 412)

Example 406. (*E2*)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 413)



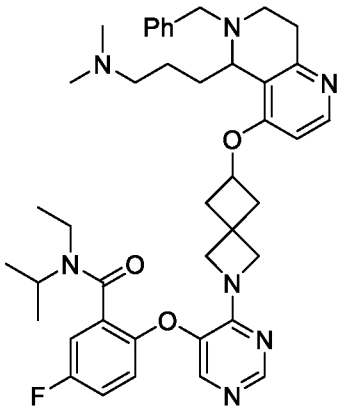
Step 1. (±)-3-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylpropan-1-amine



In a 25 mL round bottom flask, (±)-*tert*-butyl 6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1.4 g, 2.69 mmol) was added in DCM (14 mL). To this solution, TFA (0.829 mL, 10.75 mmol) was added at 0 °C. The reaction was stirred at RT for 2h. The reaction was monitored by TLC

(10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude was dissolved in 10% KOH (50 mL) and the mixture was extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford crude (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropan-1-amine (1.1 g, 97% yield) as a sticky liquid. This material was used without further purification. LCMS (Method B): Rt = 0.36 to 0.50 min, m/z = 421.6 $[M+H]^+$, 99.31%.

Step 2. (±)-2-((4-(6-((6-Benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

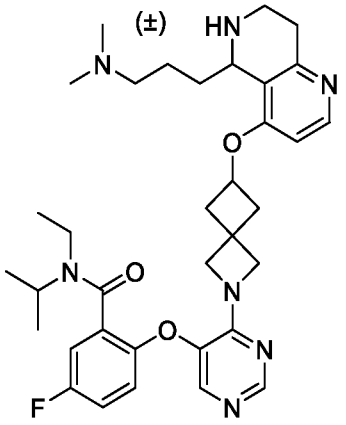


Step 2 was performed following the same procedure in two batches (800 mg and 120 mg).

To a stirred solution of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.8 g, 2.368 mmol) in IPA (8 mL), (±)-3-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylpropan-1-amine (1.083 g, 2.57 mmol) and triethylamine (0.990 mL, 7.11 mmol) were added at RT. The reaction was stirred at 80 °C for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude products from both batches were combined and purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to afford (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-

azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.6 g, 31.26% combined yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.20 (d, J = 5.7 Hz, 1H), 7.76 - 7.63 (m, 1H), 7.35 - 7.20 (m, 7H), 7.12 - 7.00 (m, 1H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 - 4.71 (m, 1H), 4.46 - 4.04 (m, 4H), 3.79 - 3.65 (m, 3H), 3.51 (d, J = 13.3 Hz, 1H), 3.44 - 3.36 (m, 1H), 3.27 - 3.11 (m, 2H), 2.98 - 2.72 (m, 4H), 2.48 - 2.43 (m, 1H), 2.23 - 2.07 (m, 4H), 2.04 (s, 6H), 1.61 - 1.44 (m, 4H), 1.22 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.93 min, m/z = 722.3 $[M+H]^+$, 99.16%.

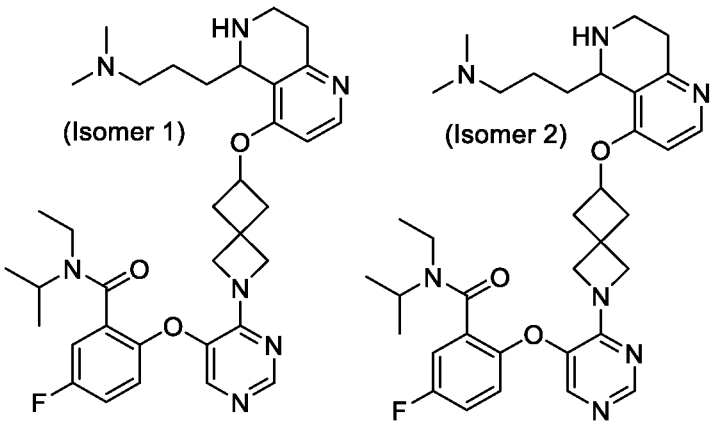
Step 3. (±)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a stirred solution of (±)-2-((4-(6-((6-benzyl-5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (600 mg, 0.831 mmol) in 2,2,2-trifluoroethanol (10 mL), Pd/C (442 mg, 4.16 mmol) was added at RT. The reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (20% MeOH in DCM). The reaction was filtered through a Celite® pad, the pad was washed with 2,2,2-trifluoroethanol (2 x 50 mL), and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure to afford (±)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (500

mg, 92% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.14 (d, *J* = 5.5 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.34 - 7.21 (m, 2H), 7.11 - 7.01 (m, 1H), 6.63 (d, *J* = 5.5 Hz, 1H), 4.78 - 4.69 (m, 1H), 4.47 - 4.06 (m, 4H), 3.84 (br d, *J* = 6.2 Hz, 1H), 3.79 - 3.69 (m, 1H), 3.46 - 3.37 (m, 1H), 3.28 - 3.20 (m, 1H), 3.07 - 2.95 (m, 1H), 2.94 - 2.86 (m, 1H), 2.86 - 2.75 (m, 2H), 2.72 - 2.60 (m, 2H), 2.30 - 2.13 (m, 5H), 2.10 (s, 6H), 1.64 - 1.42 (m, 4H), 1.26 - 0.96 (m, 9H); LCMS (Method G): Rt = 1.59 min, m/z = 632.2 $[M+H]^+$, 97.06%; Chiral SFC (Method AAM): Peak 1: Rt = 2.09 min, 53.22%; Peak 2: Rt = 5.05 min, 46.78%.

Step 4. (E1)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

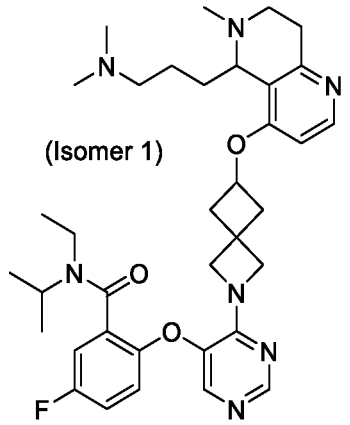


(±)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (500 mg, 0.791 mmol) was purified by chiral Prep SFC (Method AF). The product fractions were concentrated under reduced pressure to obtain (*E1*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (230 mg, 45.3% yield) and (*E2*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (200 mg, 39.1% yield) as solids.

Isomer 1. LCMS (Method G): Rt = 1.65 min, m/z = 632.3 $[M+H]^+$, 98.49%; Chiral SFC (Method AAM): Rt = 2.12 min, 100%.

Isomer 2. LCMS (Method G): Rt = 1.67 min, m/z = 632.3 $[M+H]^+$, 97.64%; Chiral SFC (Method AAM): Rt = 5.19 min, 100%.

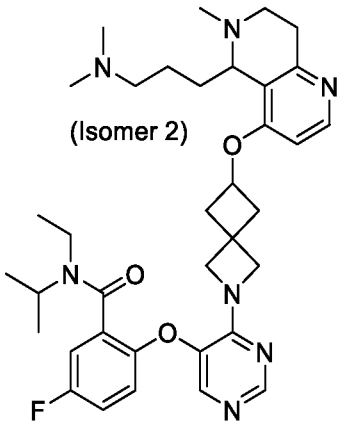
Step 5. (E1)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



In a 25 mL round bottom flask under a nitrogen atmosphere, (*E1*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (230 mg, 0.364 mmol) was added in MeOH (2.5 mL). To this solution, formaldehyde (0.136 mL, 1.820 mmol, 37% in H_2O) and AcOH (0.021 mL, 0.364 mmol) were added. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (154 mg, 0.728 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to afford (*E1*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (124.1 mg, 51.8% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.24 (m, 1H), 8.20 - 8.13 (m, 1H), 7.78 - 7.65 (m, 1H), 7.35 -

7.21 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.79 - 4.70 (m, 1H), 4.45 - 4.08 (m, 4H), 3.81 - 3.69 (m, 1H), 3.59 - 3.52 (m, 1H), 3.45 - 3.37 (m, 1H), 3.28 - 3.09 (m, 2H), 2.90 - 2.70 (m, 4H), 2.32 (s, 3H), 2.30 - 2.13 (m, 4H), 2.08 (s, 6H), 1.58 - 1.46 (m, 4H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.75 min, m/z = 646.5 $[M+H]^+$; HPLC (Method G): Rt = 4.70 min, 99.62%; Chiral SFC (Method AAM): Rt = 2.24 min, 100%.

Step 6. (E2)-2-((4-(6-((5-(3-(Dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

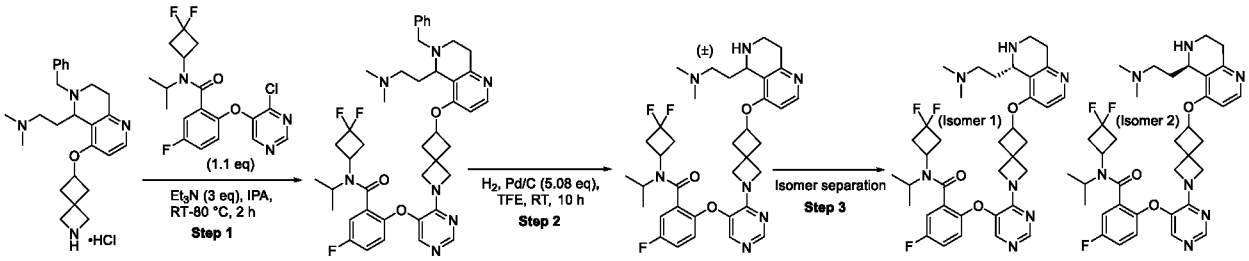


In a 100 mL round bottom flask under a nitrogen atmosphere, (*E2*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.2 g, 0.317 mmol) was added in MeOH (2.5 mL). To this solution, formaldehyde (0.128 g, 1.583 mmol, 37% in H_2O) and AcOH (0.019 g, 0.317 mmol) were added. The reaction was stirred at RT for 1 h. To this reaction mixture, sodium triacetoxyborohydride (0.134 g, 0.633 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford (*E2*)-2-((4-(6-((5-(3-(dimethylamino)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (161 mg, 78% yield) as a solid.

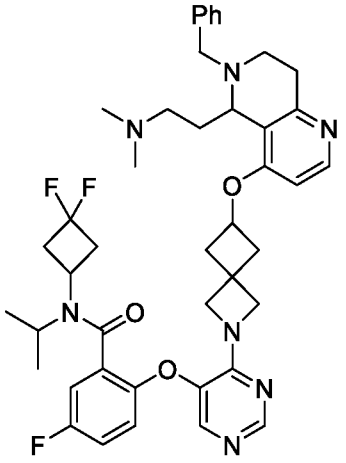
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.20 - 8.13 (m, 1H), 7.77 - 7.63 (m, 1H), 7.34 - 7.25 (m, 2H), 7.11 - 7.01 (m, 1H), 6.70 - 6.62 (m, 1H), 4.80 - 4.68 (m, 1H), 4.46 - 4.08 (m, 4H), 3.81 - 3.68 (m, 1H), 3.60 - 3.51 (m, 1H), 3.46 - 3.37 (m, 1H), 3.29 - 3.09 (m, 2H), 2.90 - 2.69 (m, 4H), 2.32 (s, 3H), 2.29 - 2.13 (m, 4H), 2.08 (s, 6H), 1.59 - 1.45 (m, 4H), 1.23 - 0.95 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.71 min, m/z = 646.3 $[M+H]^+$; HPLC (Method G): Rt = 4.70 min, 99.48%; Chiral SFC (Method AAM): Rt = 2.01 min, 100%.

Example 407. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 313)

Example 408. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 314)



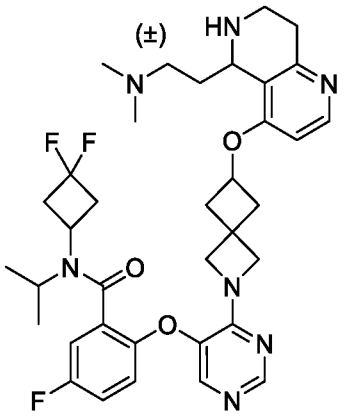
Step 1. (±)-2-((4-(6-((6-Benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1 equivalent of (±)-2-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylethan-1-amine hydrochloride and 1.1 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 3 equivalents of Et_3N was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to afford (±)-2-((4-(6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 34.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.38 - 7.21 (m, 7H), 7.06 (dd, J = 4.5, 9.1 Hz, 1H), 6.69 (d, J = 5.8 Hz, 1H), 4.80 - 4.71 (m, 1H), 4.36 - 4.02 (m, 3H), 3.96 - 3.85 (m, 1H), 3.84 - 3.79 (m, 1H), 3.77 - 3.64 (m, 3H), 3.58 - 3.46 (m, 2H), 3.30 - 3.27 (m, 1H), 3.23 - 3.11 (m, 1H), 3.00 - 2.87 (m, 1H), 2.85 - 2.58 (m, 5H), 2.47 - 2.36 (m, 2H), 2.35 - 2.15 (m, 3H), 2.11 (s, 6H), 1.79 - 1.52 (m, 2H), 1.09 (br d, J = 6.3 Hz, 3H), 1.00 (br d, J = 5.6 Hz, 3H); LCMS (Method G): Rt = 2.32 min, m/z = 770.7 $[M+H]^+$, 99.42%.

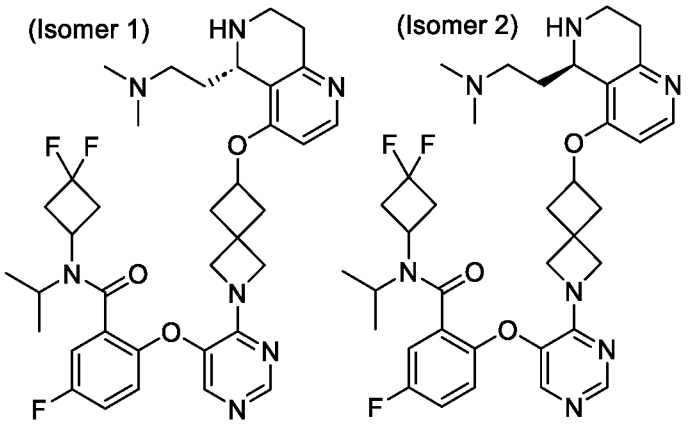
Step 2. (±)-N-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (±)-2-((4-(6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 5.08 equivalents of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure to obtain crude (±)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide. This material was used without further purification.

Yield: Quantitative; LCMS (Method G): Rt = 1.67 min, m/z = 680.4 $[M+H]^+$; HPLC (Method A): Rt = 4.70 min, 96.89%; Chiral SFC (Method AAI): Peak 1: Rt = 2.38 min, 49.71%; Peak 2: Rt = 5.34 min, 50.29%.

Step 3. (E1)-N-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide and (E2)-N-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide



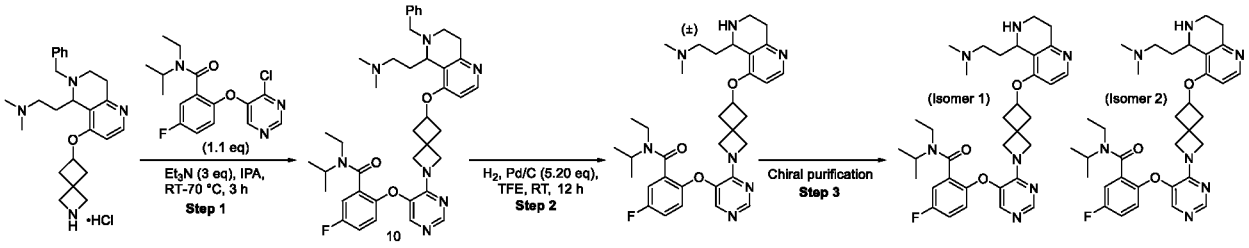
(±)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (600 mg) was purified by chiral Prep SFC (Method AB) to obtain both isomers, (*E1*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (140 mg) and (*E2*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (137 mg) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.78 (s, 1H), 7.36 (dd, J = 2.9, 8.2 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.07 (br dd, J = 4.1, 8.9 Hz, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.74 (quin, J = 6.4 Hz, 1H), 4.37 - 4.04 (m, 4H), 4.00 - 3.85 (m, 2H), 3.80 - 3.45 (m, 3H), 3.07 - 2.86 (m, 2H), 2.85 - 2.61 (m, 6H), 2.45 - 2.39 (m, 1H), 2.30 - 2.18 (m, 3H), 2.14 (s, 6H), 1.82 - 1.68 (m, 1H), 1.65 - 1.53 (m, 1H), 1.50 - 1.25 (m, 1H), 1.10 (br d, J = 5.9 Hz, 3H), 1.00 (br d, J = 5.9 Hz, 3H); LCMS (Method G): Rt = 1.81 min, m/z = 680.6 $[M+H]^+$; HPLC (Method A): Rt = 4.88 min, 98.22%; Chiral SFC (Method AAI): Rt = 2.52 min, 99.07%.

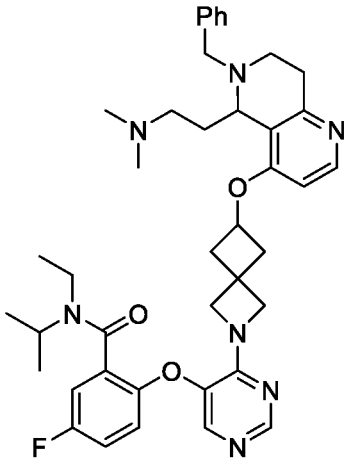
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.78 (s, 1H), 7.40 - 7.21 (m, 2H), 7.13 - 7.02 (m, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.74 (quin, J = 6.4 Hz, 1H), 4.38 - 4.04 (m, 4H), 4.02 - 3.86 (m, 2H), 3.80 - 3.46 (m, 3H), 3.08 - 2.87 (m, 2H), 2.85 - 2.61 (m, 6H), 2.46 - 2.39 (m, 1H), 2.31 - 2.18 (m, 3H), 2.14 (s, 6H), 1.81 - 1.67 (m, 1H), 1.65 - 1.50 (m, 1H), 1.49 - 1.26 (m, 1H), 1.10 (br d, J = 5.9 Hz, 3H), 1.00 (br d, J = 5.6 Hz, 3H); LCMS (Method D): Rt = 1.64 min, m/z = 680.3 $[M+H]^+$; HPLC (Method A): Rt = 4.87 min, 97.02%; Chira SFC (Method AAI): Rt = 5.21 min, 99.90%.

Example 409. (*E1*)-2-((4-(6-((5-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 328)

Example 410. (*E2*)-2-((4-(6-((5-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 329)



Step 1. (±)-2-((4-(6-((6-Benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

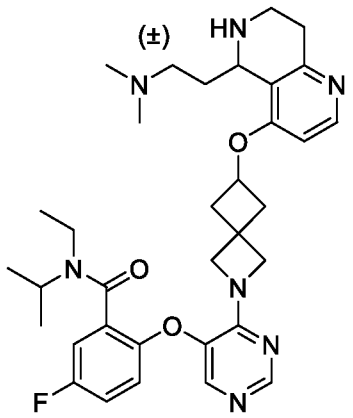


This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1.1 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 1 equivalent of (±)-2-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylethan-1-amine hydrochloride and 3 equivalents of Et_3N were used. The reaction was

stirred at 70 °C. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (50 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-2-((4-(6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 39.3%; LCMS (Method G): Rt = 2.11 min, m/z = 708.6 $[M+H]^+$, 98.10%.

Step 2. (±)-2-((4-(6-((5-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

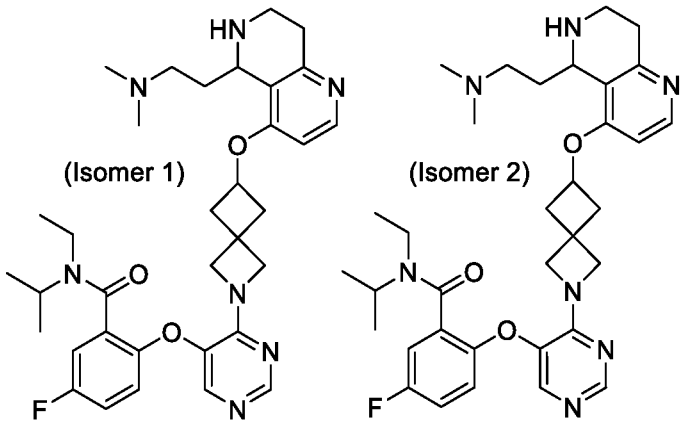


This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (±)-2-((4-(6-((6-benzyl-5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 5.2 equivalents of Pd/C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide.

Yield: 51.9%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 - 8.23 (m, 1H), 8.18 - 8.11 (m, 1H), 7.77 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 6.97 (m, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.79 - 4.71 (m, 1H), 4.31 - 4.05 (m, 4H), 4.01 - 3.90 (m, 1H), 3.75 (spt, J = 6.6 Hz, 1H), 3.46 - 3.37 (m, 1H), 3.27 - 3.13 (m, 2H), 3.07 - 2.96 (m, 1H), 2.96 - 2.88 (m, 1H), 2.85 - 2.75 (m, 2H), 2.73 - 2.57 (m, 2H), 2.47 - 2.37 (m, 1H), 2.31 - 2.17 (m, 3H), 2.14 (s, 6H), 1.82 - 1.68 (m,

1H), 1.63 - 1.40 (m, 1H), 1.25 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.63 min, m/z = 618.3 $[M+H]^+$, 99.72%; Chiral SFC (Method AAH) = Peak 1: Rt = 2.80 min, 50.47%; Peak 2: Rt = 5.37 min, 49.36%.

Step 3. (E1)-2-((4-(6-((5-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



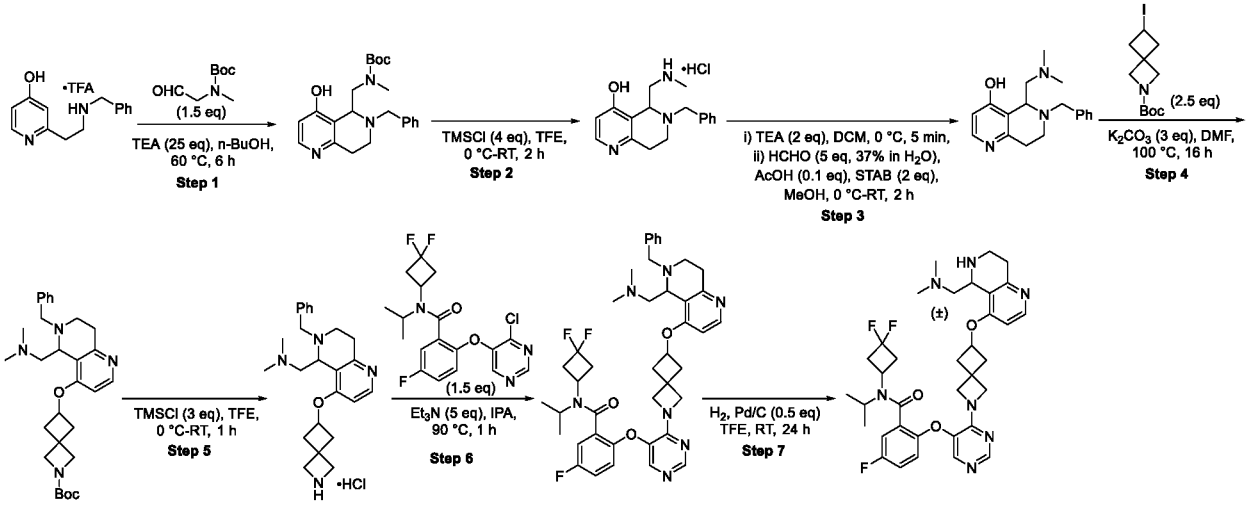
(±)-2-((4-(6-((5-(2-(Dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (290 mg) was purified by chiral Prep SFC (Method AN) to obtain both isomers, (*E1*)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (71.33 mg) and (*E2*)-2-((4-(6-((5-(2-(dimethylamino)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (76.97 mg) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.77 - 7.64 (m, 1H), 7.35 - 7.21 (m, 2H), 7.13 - 7.00 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.83 - 4.67 (m, 1H), 4.34 - 4.05 (m, 4H), 3.95 (br d, J = 9.3 Hz, 1H), 3.75 (spt, J = 6.5 Hz, 1H), 3.47 - 3.37 (m, 1H), 3.28 - 3.10 (m, 2H), 3.08 - 2.86 (m, 2H), 2.85 - 2.75 (m, 2H), 2.71 - 2.59 (m, 2H), 2.47 - 2.39 (m, 1H), 2.32 - 2.18 (m, 3H), 2.14 (s, 6H), 1.82 - 1.68 (m, 1H), 1.66 - 1.52 (m, 1H), 1.29 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.64 min, m/z = 618.4 $[M+H]^+$;

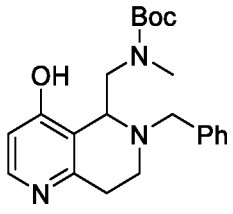
HPLC (Method A): Rt = 4.29 min, 99.13%; Chiral SFC (Method AAH): Rt = 2.98 min, 99.61%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.18 - 8.13 (m, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.21 (m, 2H), 7.12 - 7.00 (m, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.81 - 4.70 (m, 1H), 4.34 - 4.05 (m, 4H), 3.96 (br d, J = 9.6 Hz, 1H), 3.75 (spt, J = 6.5 Hz, 1H), 3.46 - 3.37 (m, 1H), 3.28 - 3.11 (m, 2H), 3.07 - 2.87 (m, 2H), 2.86 - 2.75 (m, 2H), 2.73 - 2.60 (m, 2H), 2.47 - 2.39 (m, 1H), 2.31 - 2.19 (m, 3H), 2.14 (s, 6H), 1.80 - 1.67 (m, 1H), 1.65 - 1.52 (m, 1H), 1.31 - 0.91 (m, 9H); LCMS (Method G): Rt = 1.63 min, m/z = 618.4 $[M+H]^+$; HPLC (Method A): Rt = 4.28 min, 99.42%; Chiral SFC (Method AAH): Rt = 5.97 min, 99.09%.

Example 411. (±)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 330)



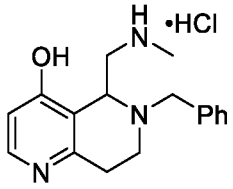
Step 1. (±)-tert-Butyl ((6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methyl)(methyl)carbamate



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 2, starting with 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid, except that 1.5 equivalents of *tert*-butyl methyl(2-oxoethyl)carbamate was used. After completion, the reaction was concentrated under reduced pressure. EtOAc was added to the residue and the mixture was washed with brine solution. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. EtOAc was added to this residue and the mixture was stirred for 15 min. The supernatant was decanted, and the resulting solid was dried under reduced pressure to obtain crude (±)-*tert*-butyl ((6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methyl)(methyl)carbamate. This material was used without further purification.

Yield: 48.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.30 (br d, J = 3.0 Hz, 1H), 7.59 - 7.48 (m, 1H), 7.40 - 7.19 (m, 5H), 5.95 (br d, J = 7.1 Hz, 1H), 3.81 - 3.66 (m, 2H), 3.60 - 3.48 (m, 2H), 3.00 (br d, J = 11.6 Hz, 1H), 2.91 - 2.69 (m, 3H), 2.61 - 2.55 (m, 3H), 2.36 - 2.20 (m, 1H), 1.52 - 1.34 (m, 9H); LCMS (Method G): Rt = 1.72 min, m/z = 384.2 $[M+H]^+$, 93.19%.

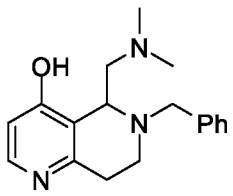
Step 2. (±)-6-Benzyl-5-((methylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 3, starting with (±)-*tert*-butyl ((6-benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methyl)(methyl)carbamate, except that 4 equivalents of TMSCl was used, to obtain crude (±)-6-benzyl-5-((methylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride. This material was used without further purification.

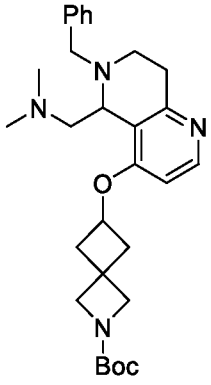
Yield: 94%; LCMS (Method D): Rt = 1.07 min, m/z = 284.2 $[M+H]^+$, 94.00%.

Step 3. (±)-6-Benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 4, starting with (±)-6-benzyl-5-((methylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol hydrochloride, except that 0.1 equivalent of AcOH was used. After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol as a solid. Yield: 39.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (br s, 1 H), 7.65 (d, J = 7.1 Hz, 1H), 7.44 – 7.25 (m, 5H), 6.10 (d, J = 7.1 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.79 – 3.65 (m, 2H), 3.26 – 2.97 (m, 4H), 2.88 – 2.72 (m, 2H), 2.55 (s, 6H); LCMS (Method G): Rt = 1.17 min, m/z = 298.1 $[M+H]^+$, 93.21%.

Step 4. (±)-tert-Butyl 6-((6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

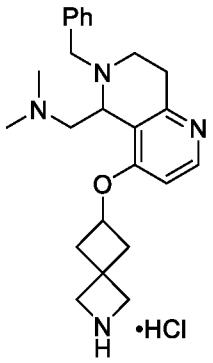


This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 5, starting with 2.5 equivalents of (±)-*tert*-butyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate, except that 1 equivalent of 6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on

Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*tert*-butyl 6-((6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate.

Yield: 18.09%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 5.6 Hz, 1H), 7.43 – 7.18 (m, 5H), 6.66 (d, J = 5.6 Hz, 1H), 4.70 (quin, J = 6.5 Hz, 1H), 4.03 (br d, J = 7.9 Hz, 1H), 3.95 – 3.77 (m, 5H), 3.65 – 3.58 (m, 1H), 3.29 – 3.16 (m, 2H), 2.95 – 2.63 (m, 5H), 2.21 (s, 6H), 2.19 – 2.09 (m, 3H), 1.37 (s, 9H); LCMS (Method G): Rt = 4.48 min, m/z = 493.3 $[M+H]^+$, 94.62%.

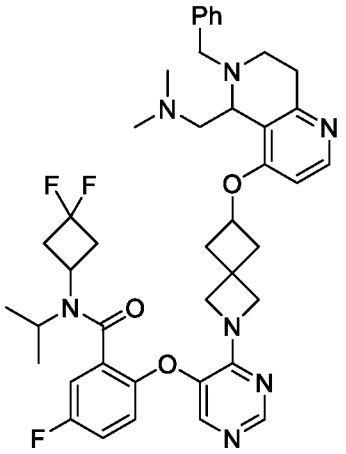
Step 5. (±)-1-(4-((2-Azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-N,N-dimethylmethanamine hydrochloride



This compound was synthesized following the procedure described for the synthesis of Intermediate 60, step 6, starting with (±)-*tert*-butyl 6-((6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, except that 3 equivalents of TMSCl was used. After completion, the reaction was concentrated under reduced pressure. The residue was triturated with EtOAc, and the supernatant was decanted. The resulting solid was dried under reduced pressure to obtain crude (±)-1-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylmethanamine hydrochloride as a solid. This material was used without further purification.

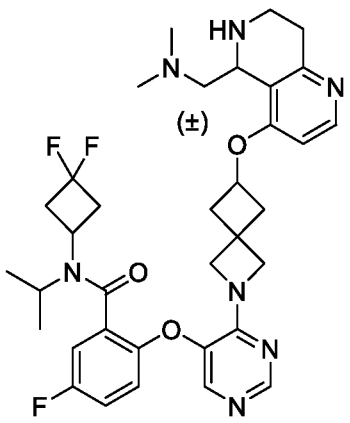
Yield: 78%; LCMS (Method B): Rt = 0.22 min, m/z = 393.4 $[M+H]^+$, 58.23%.

Step 6. (±)-2-((4-(6-((6-Benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(3,3-difluorocyclobutyl)-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 266, step 4, starting with 1 equivalent of (±)-1-(4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)-*N*,*N*-dimethylmethanamine hydrochloride and 1.5 equivalents of 2-((4-chloropyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide. The reaction was stirred at 90 °C. After completion, the reaction was concentrated under reduced pressure. The crude was purified using achiral Prep SFC (Method R) to obtain (±)-2-((4-(6-((6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide as a solid.
Yield: 30.4%. LCMS (Method G): Rt = 2.08 min, m/z = 756.3 $[M+H]^+$, 89.27%.

Step 7. (±)-N-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide

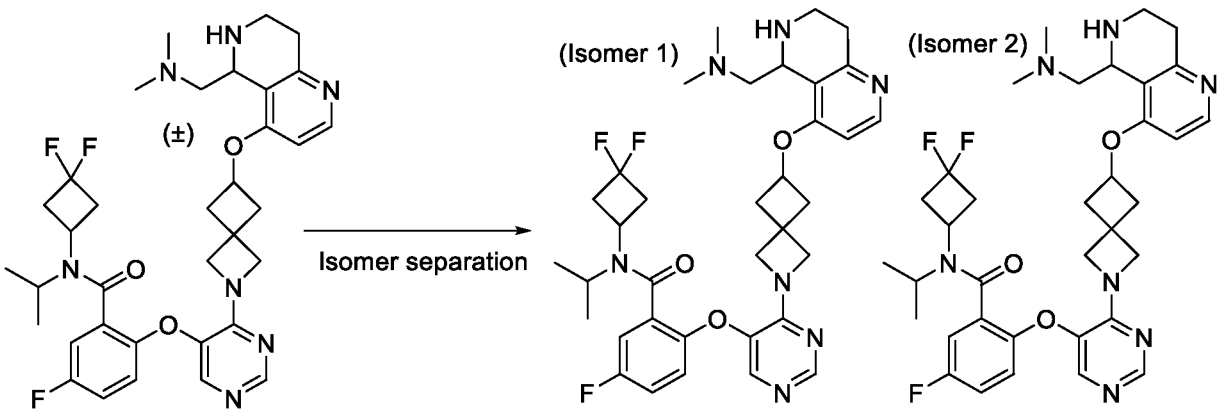


This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (±)-2-((4-(6-((6-benzyl-5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide, except that 0.5 equivalent of Pd/C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: CAN) to obtain (±)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 43.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.77 (s, 1H), 7.35 (dd, J = 2.9, 8.2 Hz, 1H), 7.27 (dt, J = 2.9, 8.6 Hz, 1H), 7.07 (br dd, J = 4.1, 8.8 Hz, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.74 (quin, J = 6.3 Hz, 1H), 4.36 – 4.00 (m, 5H), 3.98 – 3.83 (m, 1H), 3.80 – 3.46 (m, 3H), 3.12 – 3.00 (m, 1H), 2.95 – 2.55 (m, 9H), 2.31 – 2.12 (m, 9H), 1.13 – 0.94 (m, 6H); LCMS: (Method G): Rt = 1.78 min, m/z = 726.3 $[M+H]^+$; HPLC (Method A): Rt = 5.22 min, 97.56%; Chiral SFC (Method AAQ) = Peak 1: Rt = 4.81 min, 49.67%; Peak 2: Rt = 7.88 min, 48.68%.

Example 412. (*E1*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 333)

Example 413. (*E2*)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (Compound No. 334)



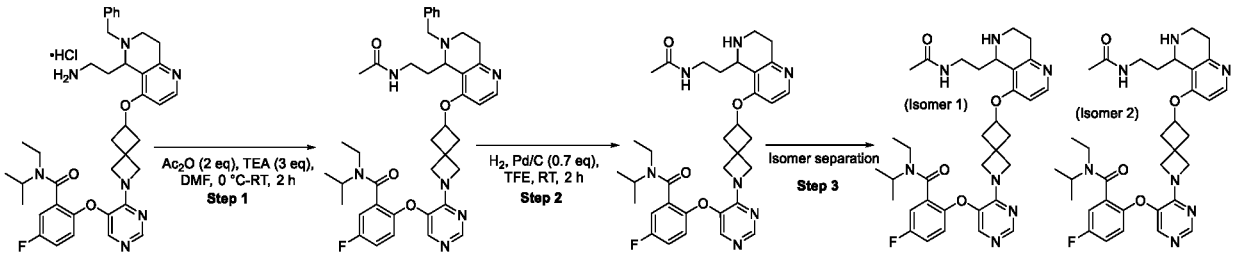
(±)-*N*-(3,3-Difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (650 mg) was purified by chiral Prep SFC (Method AM) to obtain both isomers, (*E1*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (177 mg, 53.5% yield) and (*E2*)-*N*-(3,3-difluorocyclobutyl)-2-((4-(6-((5-((dimethylamino)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (160 mg, 49.2% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.78 (s, 1H), 7.36 (dd, J = 2.9, 8.2 Hz, 1H), 7.27 (dt, J = 3.0, 8.6 Hz, 1H), 7.07 (br dd, J = 4.1, 8.9 Hz, 1H), 6.64 (d, J = 5.7 Hz, 1H), 4.74 (quin, J = 6.4 Hz, 1H), 4.39 - 3.99 (m, 5H), 3.97 – 3.83 (m, 1H), 3.80 - 3.44 (m, 3H), 3.14 - 3.01 (m, 1H), 2.96 - 2.55 (m, 9H), 2.32 - 2.11 (m, 9H), 1.14 - 0.65 (m, 6H); LCMS (Method B): Rt = 1.14 min, m/z = 666.3 $[M+H]^+$; HPLC (Method A): Rt = 5.04 min, 98.33%; Chiral SFC (Method AAQ): Rt = 4.63 min, 99.10%.

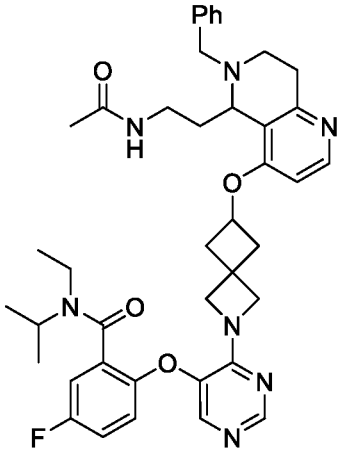
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.17 (d, J = 5.7 Hz, 1H), 7.78 (s, 1H), 7.36 (dd, J = 2.9, 8.2 Hz, 1H), 7.27 (dt, J = 3.0, 8.6 Hz, 1H), 7.07 (br dd, J = 4.1, 8.8 Hz, 1H), 6.64 (d, J = 5.7 Hz, 1H), 4.74 (quin, J = 6.3 Hz, 1H), 4.37 - 4.00 (m, 5H), 3.97 – 3.82 (m, 1H), 3.81 - 3.46 (m, 3H), 3.13 - 3.00 (m, 1H), 2.95 - 2.56 (m, 9H), 2.30 - 2.10 (m, 9H), 1.14 – 0.67 (m, 6H); LCMS (Method B): Rt = 1.11 min, m/z = 666.2 $[M+H]^+$; HPLC (Method A): Rt = 5.06 min, 99.86%; Chiral SFC (Method AAQ): Rt = 7.55 min, 99.10%.

Example 414. (*E1*)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 414)

Example 415. (*E2*)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 415)



Step 1. (±)-2-((4-(6-((5-(2-Acetamidoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

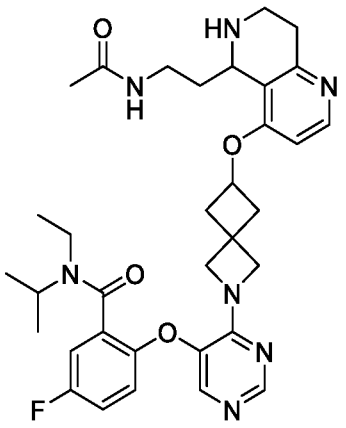


This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 1 equivalent of (±)-2-((4-(6-((5-(2-aminoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride and 2 equivalents of acetic anhydride, except that 3 equivalents of TEA was used, and DMF was used as the solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on

Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-2-((4-(6-((5-(2-acetamidoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 38.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.21 (d, J = 5.6 Hz, 1H), 7.77 - 7.64 (m, 2H), 7.40 - 7.21 (m, 7H), 7.11 - 7.00 (m, 1H), 6.69 (br d, J = 5.5 Hz, 1H), 4.81 - 4.67 (m, 1H), 4.32 - 4.04 (m, 4H), 3.80 - 3.53 (m, 4H), 3.47 - 3.38 (m, 1H), 3.27 - 3.07 (m, 4H), 3.00 - 2.85 (m, 1H), 2.84 - 2.70 (m, 3H), 2.47 - 2.41 (m, 1H), 2.32 - 2.24 (m, 1H), 2.21 - 2.13 (m, 1H), 1.81 - 1.70 (m, 4H), 1.69 - 1.58 (m, 1H), 1.26 - 0.96 (m, 9H);
LCMS (Method G): Rt = 1.84 min, m/z = 722.1 $[M+H]^+$, 95.46%.

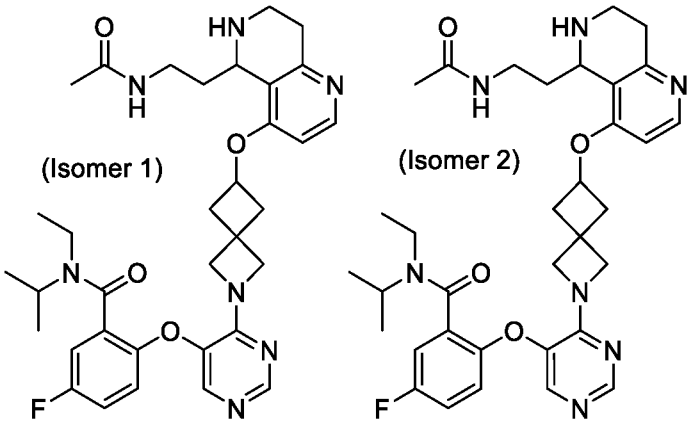
Step 2. (±)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (±)-2-((4-(6-((5-(2-acetamidoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.7 equivalent of Pd-C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure to obtain crude (±)-2-((4-(6-((5-(2-acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide. This material was used without further purification.

Yield: 58.7%; LCMS (Method G): Rt = 1.71 min, m/z = 632.4 $[M+H]^+$, 93.47%. Chiral SFC (Method AAR): Peak 1: 3.94 min, 49.88%; Peak 2: 5.04 min, 50.12%.

Step 3. (E1)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((5-(2-acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



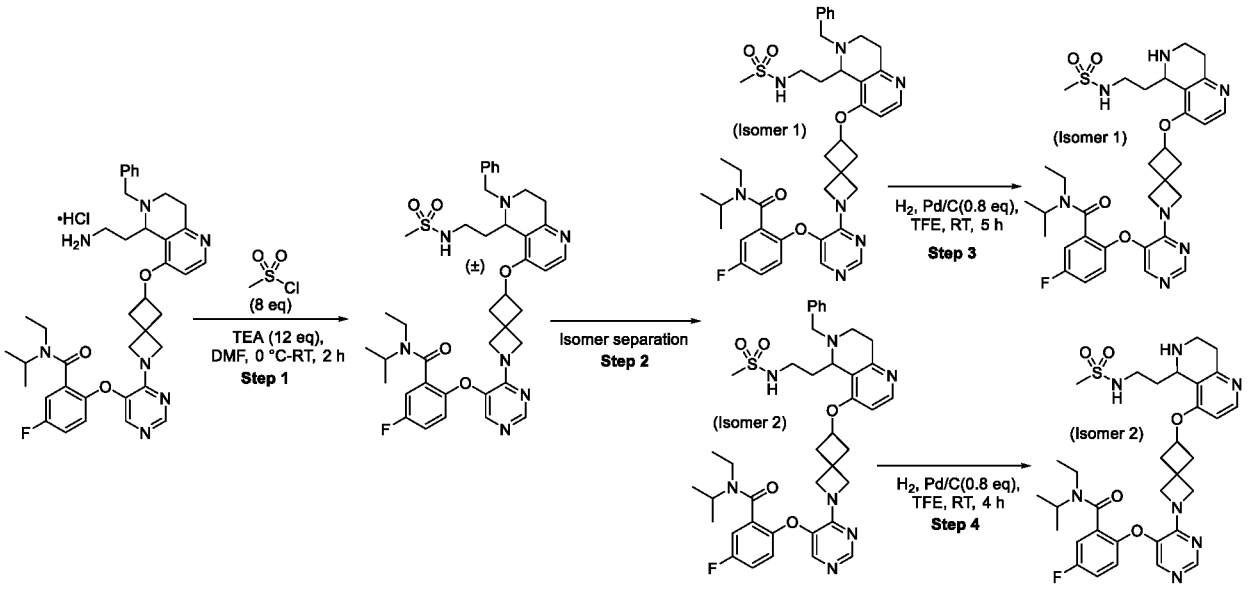
(±)-2-((4-(6-((5-(2-Acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (120 mg) was purified by chiral Prep SFC (Method AC) to obtain both isomers, (*E1*)-2-((4-(6-((5-(2-acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (40.61 mg, 33.8% yield) and (*E2*)-2-((4-(6-((5-(2-acetamidoethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (35.93 mg, 29.94% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.89 (br t, J = 5.3 Hz, 1H), 7.79 - 7.64 (m, 1H), 7.36 - 7.20 (m, 2H), 7.13 - 7.00 (m, 1H), 6.64 (br d, J = 5.5 Hz, 1H), 4.80 - 4.65 (m, 1H), 4.33 - 4.07 (m, 4H), 3.92 (br d, J = 9.5 Hz, 1H), 3.82 - 3.69 (m, 1H), 3.47 - 3.37 (m, 1H), 3.28 - 3.10 (m, 3H), 3.07 - 2.90 (m, 2H), 2.84 - 2.59 (m, 5H), 2.32 - 2.18 (m, 2H), 1.84 - 1.70 (m, 4H), 1.67 - 1.54 (m, 1H), 1.24 - 0.93 (m, 9H); LCMS (Method G): Rt = 1.45 min, m/z = 632.2 $[M+H]^+$; HPLC (Method G): Rt = 4.31 min, 99.86%; Chiral SFC (Method AAR): Rt = 4.15 min, 100%.

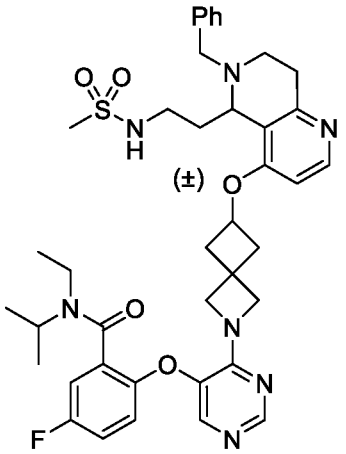
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.89 (br t, J = 5.4 Hz, 1H), 7.79 - 7.64 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 - 6.99 (m, 1H), 6.64 (br d, J = 5.5 Hz, 1H), 4.78 - 4.66 (m, 1H), 4.34 - 4.05 (m, 4H), 3.91 (br d, J = 9.4 Hz, 1H), 3.83 - 3.66 (m, 1H), 3.47 - 3.37 (m, 1H), 3.28 - 3.08 (m, 3H), 3.06 - 2.88 (m, 2H), 2.84 - 2.58 (m, 5H), 2.32 - 2.17 (m, 2H), 1.84 - 1.70 (m, 4H), 1.67 - 1.52 (m, 1H), 1.33 - 0.91 (m, 9H); LCMS (Method G): Rt = 1.44 min, m/z = 632.2 $[M+H]^+$; HPLC (Method G): Rt = 4.31 min, 99.67%; Chiral SFC (Method AAR): Rt = 5.28 min, 99.38%.

Example 416. (*E1*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 416)

Example 417. (*E2*)-*N*-Ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 417)



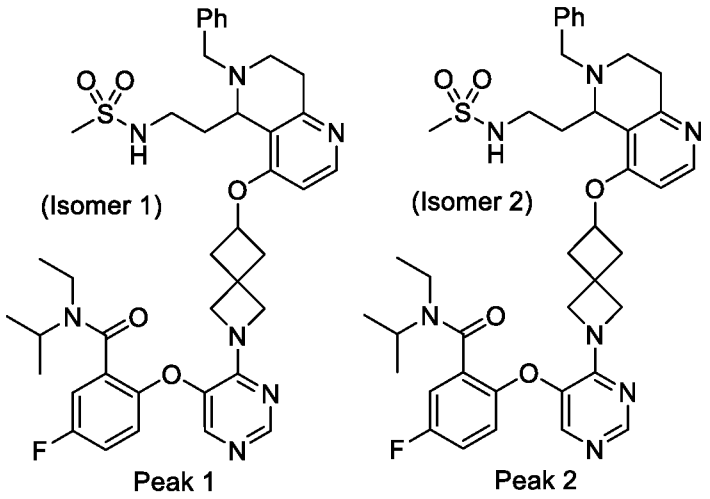
Step 1. (±)-2-((4-(6-((6-Benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 250, starting with 8 equivalents of methanesulfonyl chloride, except that 1 equivalent of (±)-2-((4-(6-((5-(2-aminoethyl)-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride, and 12 equivalents of TEA were used, and DMF was used as a solvent. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 30.0%; LCMS (Method G): Rt = 1.97 min, m/z = 758.2 $[M+H]^+$, 99.18%.

Step 2. (E1)-2-((4-(6-((6-Benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



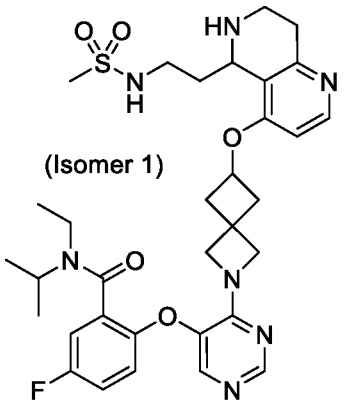
(±)-2-((4-(6-((6-Benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (240 mg) was purified by chiral Prep SFC (Method AC) to obtain both isomers, (*E1*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (90 mg, 37.5% yield) and (*E2*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (95 mg, 39.6% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.25 - 8.20 (m, 1H), 7.77 - 7.65 (m, 1H), 7.40 - 7.21 (m, 7H), 7.11 - 6.94 (m, 2H), 6.79 - 6.66 (m, 1H), 4.82 - 4.70 (m, 1H), 4.33 - 4.04 (m, 4H), 3.85 - 3.70 (m, 2H), 3.68 - 3.56 (m, 2H), 3.46 - 3.37 (m, 1H), 3.27 - 3.03 (m, 4H), 3.00 - 2.91 (m, 1H), 2.88 (s, 3H), 2.84 - 2.70 (m, 3H), 2.46 - 2.42 (m, 1H), 2.38 - 2.28 (m, 1H), 2.25 - 2.16 (m, 1H), 1.88 - 1.67 (m, 2H), 1.32 - 0.94 (m, 9H); LCMS (Method G): Rt = 1.95 min, m/z = 758.2 $[M+H]^+$, 99.61%; Chiral SFC (Method AAG): Rt = 5.86 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.26 (m, 1H), 8.25 - 8.20 (m, 1H), 7.77 - 7.65 (m, 1H), 7.40 - 7.21 (m, 7H), 7.11 - 6.94 (m, 2H), 6.76 - 6.67 (m, 1H), 4.84 - 4.70 (m, 1H), 4.33 - 4.06 (m, 4H), 3.86 - 3.70 (m, 2H), 3.69 - 3.55 (m, 2H), 3.46 - 3.37 (m, 1H), 3.28 - 3.02 (m, 4H), 3.00 - 2.92 (m, 1H), 2.88 (s, 3H), 2.84 - 2.69 (m, 3H), 2.46 - 2.42 (m, 1H), 2.37 - 2.28 (m, 1H), 2.26 - 2.16 (m, 1H), 1.89 - 1.70 (m, 2H), 1.30 - 0.94 (m, 9H); LCMS (Method

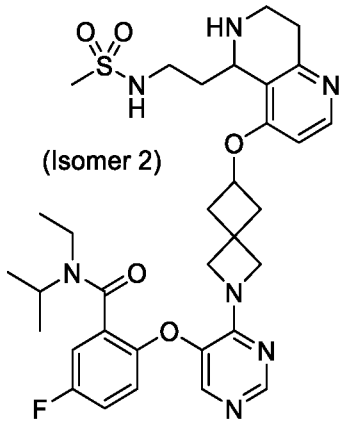
G): Rt = 1.95 min, m/z = 758.2 $[M+H]^+$, 99.45%; Chiral SFC (Method AAG: Rt = 8.09 min, 99.95%.

Step 3. (E1)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (*E1*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.8 equivalent of Pd-C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E1*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.
Yield: 53.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 - 8.25 (m, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.15 - 6.99 (m, 2H), 6.72 - 6.63 (m, 1H), 4.80 - 4.67 (m, 1H), 4.33 - 4.07 (m, 4H), 3.95 (br d, J = 8.3 Hz, 1H), 3.83 - 3.67 (m, 1H), 3.46 - 3.39 (m, 1H), 3.27 - 3.21 (m, 1H), 3.18 - 3.07 (m, 3H), 3.03 - 2.93 (m, 2H), 2.89 (s, 3H), 2.84 - 2.61 (m, 4H), 2.38 - 2.22 (m, 2H), 1.91 - 1.63 (m, 2H), 1.35 - 0.90 (m, 9H); LCMS (Method G): Rt = 1.72 min, m/z = 668.3 $[M+H]^+$; HPLC (Method G): Rt = 4.55 min, 99.34%; Chiral SFC (Method J): Rt = 3.57 min, 98.44%.

Step 4. (E2)-N-Ethyl-5-fluoro-N-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

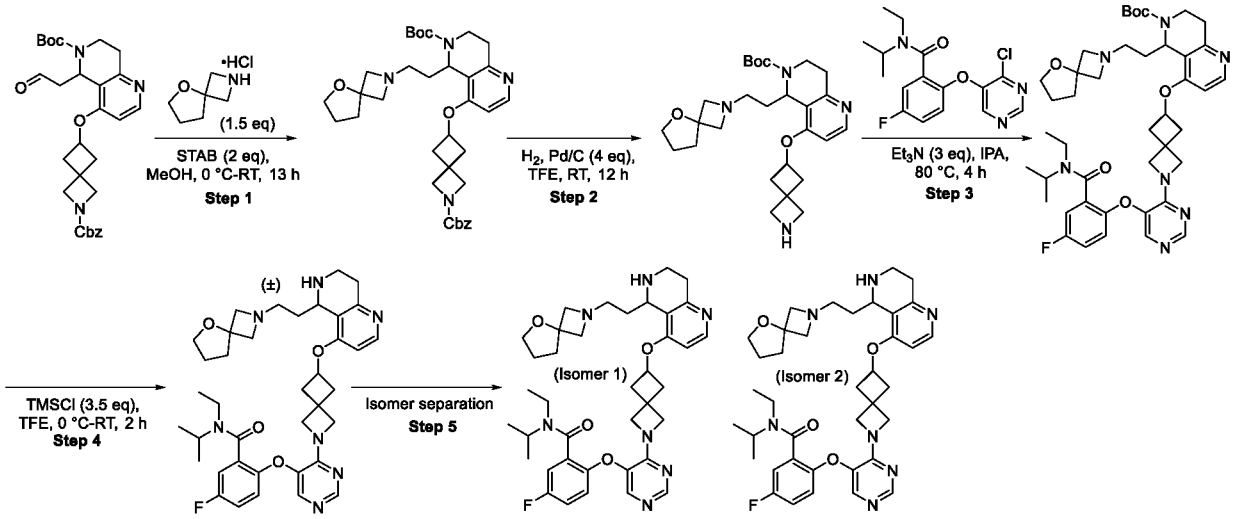


This compound was synthesized following the procedure described for the synthesis of Examples 279 and 280, step 2, starting with (*E2*)-2-((4-(6-((6-benzyl-5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide, except that 0.8 equivalent of Pd-C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford (*E2*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5-(2-(methylsulfonamido)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

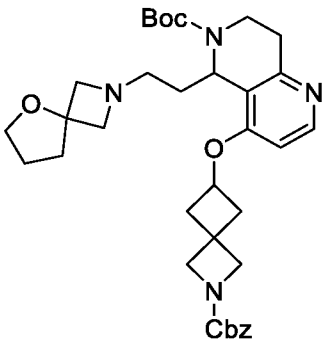
Yield: 62.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.79 - 7.65 (m, 1H), 7.35 - 7.21 (m, 2H), 7.13 - 7.01 (m, 2H), 6.72 - 6.63 (m, 1H), 4.80 - 4.69 (m, 1H), 4.32 - 4.07 (m, 4H), 4.00 - 3.88 (m, 1H), 3.75 (spt, J = 6.6 Hz, 1H), 3.48 - 3.37 (m, 1H), 3.29 - 3.21 (m, 1H), 3.19 - 3.07 (m, 3H), 2.89 (s, 3H), 2.85 - 2.61 (m, 5H), 2.37 - 2.18 (m, 3H), 1.90 - 1.62 (m, 2H), 1.30 - 0.93 (m, 9H); LCMS (Method G): Rt = 1.77 min, m/z = 668.3 $[M+H]^+$; HPLC (Method G): Rt = 4.53 min, 99.54%; Chiral SFC (Method J): Rt = 2.92 min, 100%.

Example 418. (*E1*)-2-((4-(6-((5-(2-(5-Oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 418)

Example 419. (*E2*)-2-((4-(6-((5-(2-(5-Oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 419)



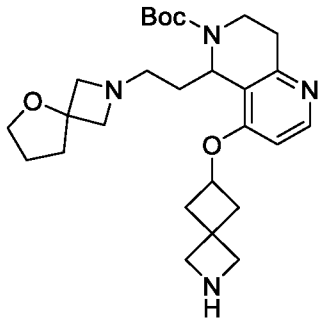
Step 1. (±)-tert-Butyl 5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This reaction was performed following the same procedure in two batches (2 x 1.4 g).

To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-oxoethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.4 g, 2.68 mmol) in MeOH (20 mL), 5-oxa-2-azaspiro[3.4]octane hydrochloride (0.602 g, 4.03 mmol) was added at RT. The reaction was stirred at RT for 1 h. STAB (1.138 g, 5.37 mmol) was then added, and the reaction was stirred at RT for 12 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction mixture from both batches were mixed and diluted with saturated $NaHCO_3$ (30 mL), and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine solution (25 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (950 mg, 18.8% combined yield) as a solid. LCMS (Method G): Rt = 1.96 min, m/z = 619.2 $[M+H]^+$, 58.45%.

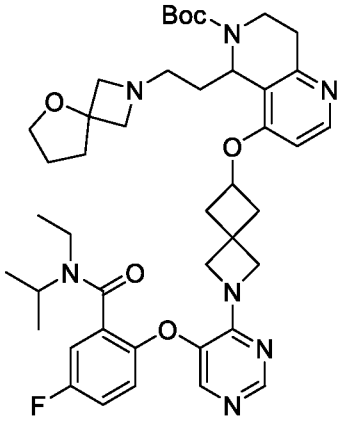
Step 2. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a solution of (±)-*tert*-butyl 5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (600 mg, 0.970 mmol) in TFE (5 mL), Pd-C (413 mg, 3.88 mmol) was added at RT. The reaction was stirred at RT for 12 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (2 x 10 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-

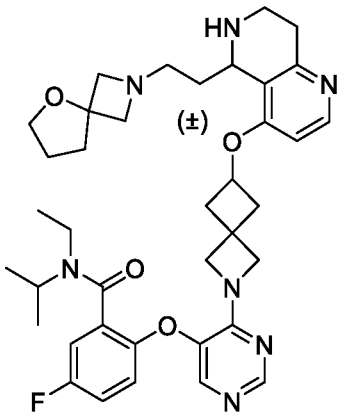
tert-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (450 mg, 53.9% yield) as a solid. This material was used without further purification. LCMS (Method G): Rt = 1.44 min, m/z = 485.2 $[M+H]^+$, 56.26%.

Step 3. (±)-tert-Butyl 5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



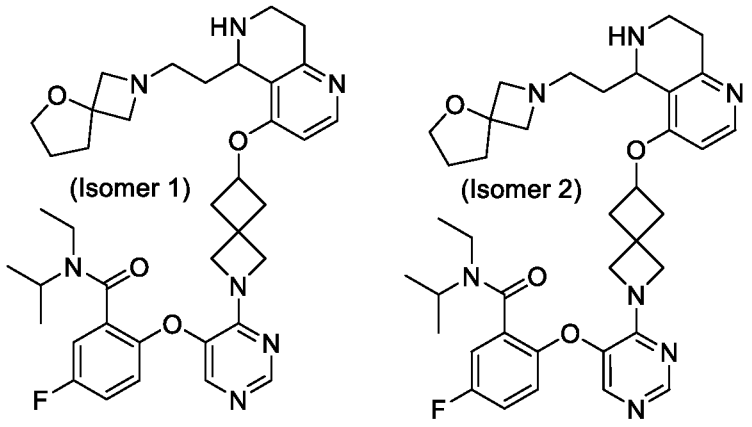
To a stirred solution of (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (450 mg, 0.929 mmol) in IPA (5 mL), 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (314 mg, 0.929 mmol) and TEA (0.391 mL, 2.79 mmol) were added at RT. The reaction was stirred at 80 °C for 4 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (350 mg, 32.4% yield) as a solid. LCMS (Method G): Rt = 2.11 min, m/z = 786.4 $[M+H]^+$, 67.62%.

Step 4. (±)-2-((4-(6-((5-(2-(5-Oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a solution of (±)-*tert*-butyl 5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (300 mg, 0.382 mmol) in TFE (5 mL), TMSCl (0.170 mL, 1.336 mmol) was added at 0 °C. The reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((4-(6-((5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (142 mg, 54.2% yield) as a solid. LCMS (Method G): Rt = 1.74 min, m/z = 686.3 $[M+H]^+$; HPLC (Method G): Rt = 4.66 min, 99.08%; Chiral SFC (Method AAU): Peak 1: Rt = 1.98 min, 48.03%; Peak 2: Rt = 3.52 min, 50.93%.

Step 5. (E1)-2-((4-(6-((5-(2-(5-Oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



(±)-2-((4-(6-((5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (142 mg) was purified by chiral Prep SFC (Method AQ) to obtain both isomers, (*E1*)-2-((4-(6-((5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (37.64 mg, 26.5% yield) and (*E2*)-2-((4-(6-((5-(2-(5-oxa-2-azaspiro[3.4]octan-2-yl)ethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (35.15 mg, 24.75% yield) as solids.

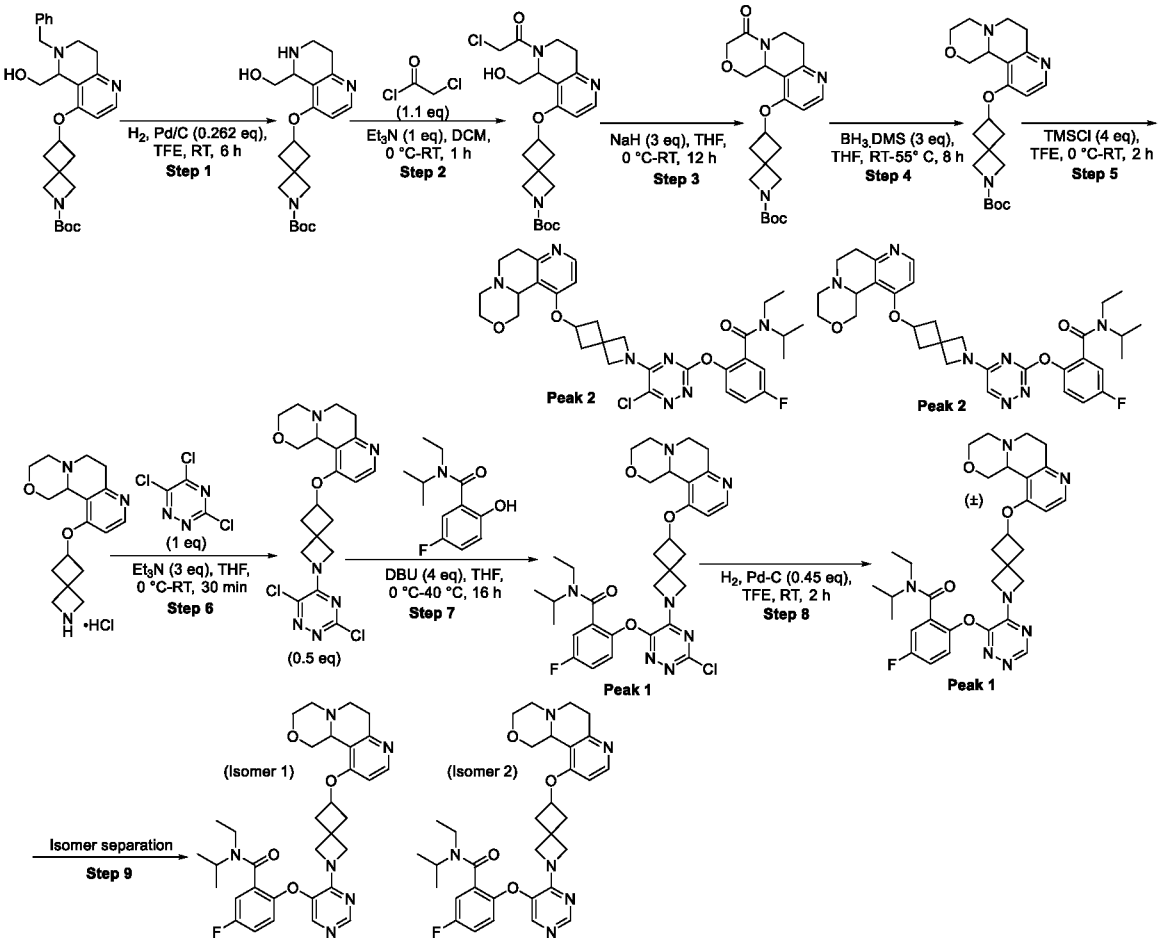
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.19 - 8.10 (m, 1H), 7.77 - 7.63 (m, 1H), 7.35 - 7.23 (m, 2H), 7.13 - 7.01 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.80 - 4.69 (m, 1H), 4.32 - 4.07 (m, 4H), 3.93 (br d, J = 8.0 Hz, 1H), 3.75 (spt, J = 6.6 Hz, 1H), 3.64 (t, J = 6.7 Hz, 2H), 3.44 - 3.37 (m, 1H), 3.26 (br t, J = 6.9 Hz, 2H), 3.22 - 3.13 (m, 1H), 3.05 - 2.95 (m, 1H), 2.94 - 2.85 (m, 3H), 2.85 - 2.74 (m, 2H), 2.73 - 2.52 (m, 4H), 2.29 - 2.16 (m, 2H), 2.01 - 1.94 (m, 2H), 1.78 (quin, J = 6.9 Hz, 2H), 1.63 - 1.44 (m, 2H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.62 min, m/z = 686.2 $[M+H]^+$; HPLC (Method G): Rt = 4.68 min, 99.61%; Chiral SFC (Method AAU): Rt = 2.10 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 - 8.25 (m, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.77 - 7.64 (m, 1H), 7.35 - 7.22 (m, 2H), 7.12 - 7.01 (m, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.79 - 4.70 (m, 1H), 4.33 - 4.08 (m, 4H), 3.94 (br d, J = 8.1 Hz, 1H), 3.75 (spt, J = 6.6, 13.2 Hz, 1H), 3.64 (t, J = 6.7 Hz, 2H), 3.45 - 3.38 (m, 1H), 3.29 - 3.22 (m, 2H), 3.21 - 3.12 (m, 1H), 3.05 - 2.96 (m, 1H), 2.95 - 2.85 (m, 3H), 2.85 - 2.76 (m, 2H), 2.73 - 2.53 (m, 4H), 2.29 - 2.16

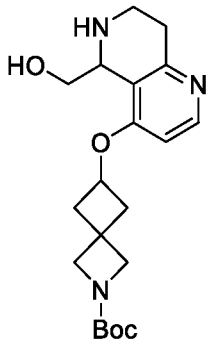
(m, 2H), 2.02 - 1.93 (m, 2H), 1.79 (quin, *J* = 6.9 Hz, 2H), 1.61 - 1.48 (m, 2H), 1.22 - 0.96 (m, 9H), one proton merged with solvent peaks; LCMS (Method B): Rt = 0.94 min, m/z = 686.4 $[M+H]^+$; HPLC (Method G): Rt = 4.69 min, 98.54%; Chiral SFC (Method AAU): Rt = 3.84 min, 100%.

Example 420. (*E1*)-*N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (Compound No. 420)

Example 421. (*E2*)-*N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (Compound No. 421)

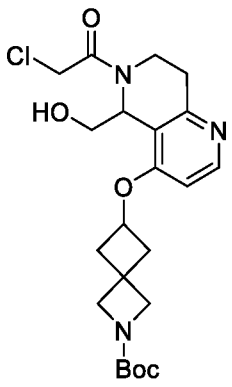


Step 1. (±)-tert-Butyl 6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



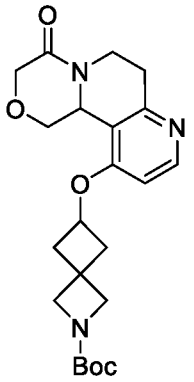
In a 100 mL round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 6-((6-benzyl-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (5.84 g, 12.54 mmol) was added in 2,2,2-trifloroethanol (50 mL). To this solution, Pd-C (3.50 g, 3.29 mmol) was added, and the reaction was stirred at RT for 6 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted in 10-15% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphth,yridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (3.85 g, 81% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (d, J = 5.6 Hz, 1H), 6.66 (d, J = 5.8 Hz, 1H), 4.76 - 4.66 (m, 2H), 4.02 - 3.96 (m, 1H), 3.91 (br s, 2H), 3.85 (br s, 2H), 3.62 - 3.56 (m, 1H), 3.50 - 3.43 (m, 1H), 3.16 - 3.08 (m, 1H), 2.96 - 2.88 (m, 1H), 2.80 - 2.70 (m, 4H), 2.33-2.20 (m, 2H), 1.37 (s, 9H), one proton merged with solvent peak; LCMS (Method B): Rt = 0.96 min, m/z = 376.4 $[M+H]^+$, 99.54%.

Step 2. (±)-tert-Butyl 6-((6-(2-chloroacetyl)-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-*tert*-butyl 6-((5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (3.85 g, 10.25 mmol) in DCM (60 mL), triethylamine (1.429 mL, 10.25 mmol) was added at 0 °C. To this reaction mixture, 2-chloroacetyl chloride (0.897 mL, 11.28 mmol) was added slowly, and the reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude (±)-*tert*-butyl 6-((6-(2-chloroacetyl)-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (4.88 g, 84% yield). LCMS (Method B): Rt = 1.32 min, m/z = 452.1 $[M+H]^+$; 79.57%. This material was used without further purification.

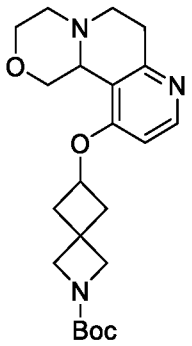
Step 3. (±)-tert-Butyl 6-((4-oxo-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



In a 100 mL two neck round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 6-((6-(2-chloroacetyl)-5-(hydroxymethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (4.88 g, 4.98 mmol) was dissolved in THF (50 mL). To this solution, NaH (0.597 g, 14.93 mmol) was added at 0 °C, and the reaction was stirred at RT for 12 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was cooled to 0 °C, quenched with water (50 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column

chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain (±)-*tert*-butyl 6-((4-oxo-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (3.55 g, 73.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (d, J = 5.5 Hz, 1H), 6.79 (d, J = 5.6 Hz, 1H), 5.02 (dd, J = 3.9, 9.8 Hz, 1H), 4.80 - 4.72 (m, 3H), 4.67 (dd, J = 4.0, 11.3 Hz, 1H), 4.26 - 4.19 (m, 1H), 4.13 - 4.06 (m, 1H), 3.91 (br s, 2H), 3.85 (br s, 2H), 2.86 - 2.67 (m, 5H), 2.27-2.24 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 1.60 min, m/z = 416.0 $[M+H]^+$, 93.53%.

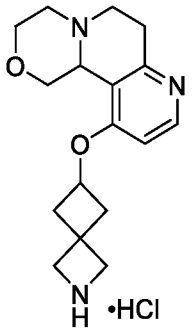
Step 4. (±)-tert-Butyl 6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of (±)-*tert*-butyl 6-((4-oxo-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (3.5 g, 8.42 mmol) in THF (35 mL), borane dimethylsulfide complex (25.3 mL, 25.3 mmol, 1M in THF) was added at 0 °C under a nitrogen atmosphere. The reaction was stirred at 55 °C for 8 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was cooled to 0 °C and quenched with methanol (50 mL), and the mixture was stirred at 55 °C for 12 h. The reaction was cooled to RT and concentrated under reduced pressure. Water (25 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain (±)-*tert*-butyl 6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (2.8 g, 80% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, J = 5.6 Hz, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.74 - 4.66 (m, 1H), 4.41 (dd,

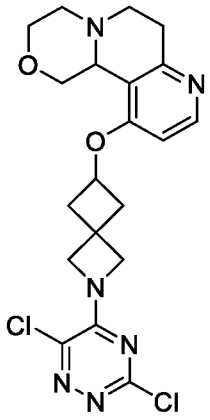
J = 2.7, 10.6 Hz, 1H), 3.91 (br s, 2H), 3.84 (br s, 2H), 3.69 - 3.57 (m, 2H), 3.22 - 3.15 (m, 1H), 3.12 - 3.05 (m, 1H), 3.02 - 2.92 (m, 1H), 2.84 - 2.79 (m, 2H), 2.79 - 2.64 (m, 4H), 2.61 - 2.53 (m, 1H), 2.25 - 2.17 (m, 2H), 1.37 (s, 9H); LCMS (Method G): Rt = 1.95 min, m/z = 402.3 $[M+H]^+$, 97.15%.

Step 5. (±)-11-((2-Azaspiro[3.3]heptan-6-yl)oxy)-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridine hydrochloride



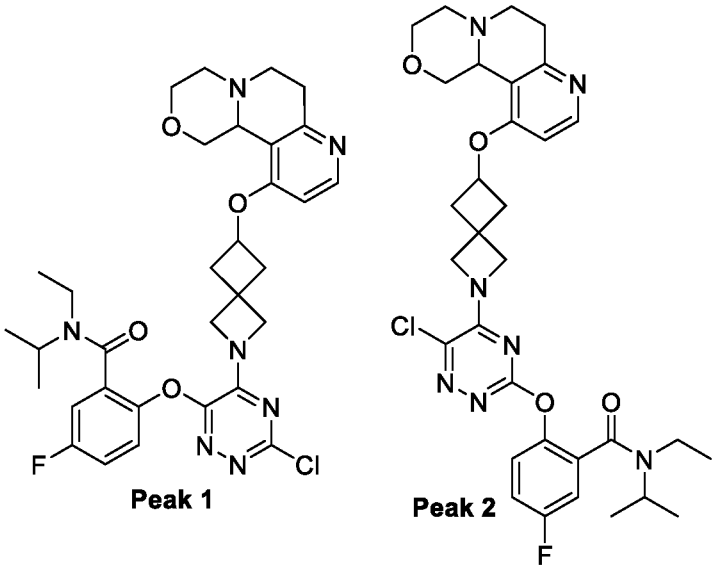
To a stirred solution of (±)-*tert*-butyl 6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (2.38 g, 5.93 mmol) in 2,2,2-trifluoroethanol (23 mL), TMSCl (3.01 mL, 23.71 mmol) was added slowly at 0 °C. The reaction was stirred at RT for 2 h. The progress of the reaction was monitored by TLC (10% MeOH in EtOAc). After completion, the reaction was concentrated under reduced pressure. The crude was triturated with EtOAc (2 x 25 mL), and the supernatant was decanted. The solid was dried under vacuum to obtain (±)-11-((2-azaspiro[3.3]heptan-6-yl)oxy)-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridine hydrochloride (2.0 g, 93% yield) as a solid. LCMS (Method G): Rt = 0.95 min, m/z = 302.0 $[M+H]^+$, 93.31%.

Step 6. (±)-11-((2-(3,6-Dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridine



To a stirred solution of (±)-11-((2-azaspiro[3.3]heptan-6-yl)oxy)-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridine hydrochloride (2.0 g, 5.92 mmol) in DCM (20 mL) under a nitrogen atmosphere, Et_3N (2.475 mL, 17.76 mmol) was added at 0 °C. To this reaction mixture, 3,5,6-trichloro-1,2,4-triazine (1.092 g, 5.92 mmol) was added, and the reaction was stirred at RT for 30 minutes. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was quenched with water (25 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain (±)-11-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridine (2.0 g, 60.5% yield) as a solid. LCMS (Method G): Rt = 1.84 min, m/z = 449.1 $[M+H]^+$, 80.52%.

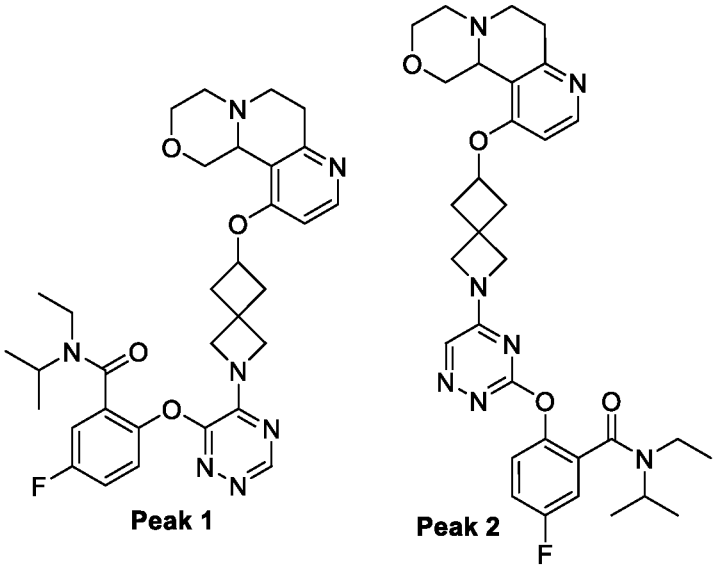
Step 7. (±)-2-((6-Chloro-5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (±)-2-((3-chloro-5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



To a stirred solution of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (1.2 g, 5.33 mmol) in THF (15 mL), DBU (3.21 mL, 21.31 mmol) was added at 0 °C. To this reaction mixture, (±)-11-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridine (1.197 g, 2.66 mmol) was added at 0 °C, and the reaction was stirred at 40 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using EtOAc in hexane (the product was eluted at 100% EtOAc) to obtain a mixture of regioisomers, (±)-2-((6-chloro-5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and (±)-2-((3-chloro-5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (1.4 g, 39.4% yield, combined yield) as a semi-solid. LCMS (Method B): Rt = 1.42 min, m/z = 638.5 $[M+H]^+$, 95.77%.

Step 8. (±)-N-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide and (±)-N-ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-

[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-N-isopropylbenzamide



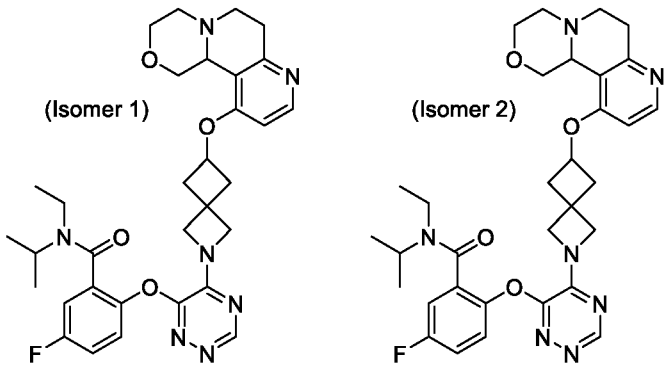
In a 100 mL round bottom flask under an argon atmosphere, a mixture of (±)-2-((6-chloro-5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide and (±)-2-((3-chloro-5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (400 mg, 0.627 mmol) was dissolved in 2,2,2-trifluororethanol (20 mL). To this solution, Pd-C (300 mg, 0.282 mmol) was added, and the reaction was stirred at RT for 2 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with 2,2,2-trifluororethanol (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain the mixture of regioisomers (250 mg, 0.414 mmol). The mixture was purified by chiral Prep SFC (Method X) to obtain both regioisomers.

Peak 1. (±)-*N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide as a solid (150 mg, 39.1% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ

8.47 (s, 1H), 8.21 (d, *J* = 5.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.39 - 7.33 (m, 2H), 6.70 (d, *J* = 5.8 Hz, 1H), 4.82 - 4.74 (m, 1H), 4.65 - 4.51 (m, 2H), 4.43 (d, *J* = 9.8 Hz, 1H), 4.32 - 4.13 (m, 2H), 3.70 - 3.58 (m, 4H), 3.20 (t, *J* = 9.8 Hz, 1H), 3.09 (dd, *J* = 5.0, 10.5 Hz, 2H), 3.05 - 2.93 (m, 2H), 2.86-2.79 (m, 4H), 2.73 - 2.69 (m, 1H), 2.62 - 2.54 (m, 2H), 2.39 - 2.34 (m, 1H), 1.15 - 0.94 (m, 7H), 0.75 - 0.68 (m, 2H); LCMS (Method G): Rt = 1.98 min, m/z = 604.3 $[M+H]^+$, 98.67%.

Peak 2. *(±)-N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-3-yl)oxy)-*N*-isopropylbenzamide as a solid (26 mg, 6.68% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 - 8.34 (m, 1H), 8.21 (d, *J* = 5.5 Hz, 1H), 7.33 - 7.23 (m, 3H), 6.69 (d, *J* = 5.8 Hz, 1H), 4.81 - 4.72 (m, 1H), 4.45 - 4.40 (m, 1H), 4.36 - 4.25 (m, 2H), 4.14 - 4.02 (m, 2H), 3.77 - 3.70 (m, 1H), 3.69 - 3.59 (m, 3H), 3.20 (t, *J* = 9.9 Hz, 1H), 3.15 - 3.06 (m, 2H), 3.03 - 2.94 (m, 1H), 2.90 - 2.76 (m, 5H), 2.69 - 2.65 (m, 1H), 2.62 - 2.56 (m, 1H), 2.37 - 2.30 (m, 2H), 1.13 - 0.86 (m, 9H); LCMS (Method B): Rt = 1.34 min, m/z = 604.3 $[M+H]^+$, 99.76%.

Step 9. (E1)-N-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide and (E2)-N-ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-isopropylbenzamide



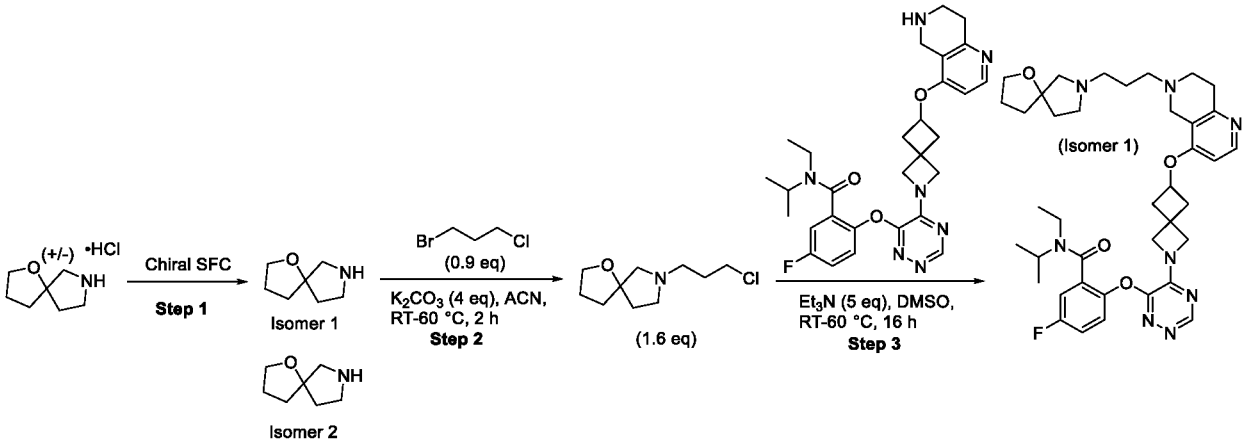
(±)-*N*-Ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (150 mg) was purified by chiral Prep SFC (Method Z) to obtain both isomers, (*E1*)-*N*-ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-

f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (46.87 mg) and (*E2*)-*N*-ethyl-5-fluoro-2-((5-(6-((1,3,4,6,7,11b-hexahydro-[1,4]oxazino[3,4-f][1,6]naphthyridin-11-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (45.66 mg) as solids.

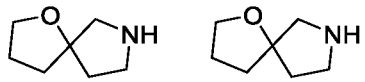
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.21 (d, J = 5.5 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.40 - 7.31 (m, 2H), 6.70 (d, J = 5.6 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.66 - 4.51 (m, 2H), 4.43 (d, J = 10.1 Hz, 1H), 4.33 - 4.13 (m, 2H), 3.70 - 3.57 (m, 4H), 3.20 (t, J = 9.9 Hz, 1H), 3.14 - 3.06 (m, 2H), 3.05 - 2.93 (m, 2H), 2.88 - 2.77 (m, 4H), 2.73-2.69 (m, 1H), 2.62 - 2.54 (m, 2H), 2.39 - 2.35 (m, 1H), 1.16 - 0.94 (m, 7H), 0.75 - 0.69 (m, 2H); LCMS (Method G): Rt = 1.58 min, m/z = 604.2 $[M+H]^+$; HPLC (Method G): Rt = 4.64 min, 97.16%; Chiral SFC (Method AX): Rt = 5.33 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.21 (d, J = 5.6 Hz, 1H), 7.47 - 7.42 (m, 1H), 7.39 - 7.32 (m, 2H), 6.70 (d, J = 5.6 Hz, 1H), 4.82 - 4.74 (m, 1H), 4.66 - 4.51 (m, 2H), 4.47 - 4.40 (m, 1H), 4.34 - 4.12 (m, 2H), 3.70 - 3.57 (m, 4H), 3.20 (br t, J = 10.1 Hz, 1H), 3.12-3.07 (m, 2H), 3.05 - 2.93 (m, 2H), 2.89 - 2.76 (m, 4H), 2.72 - 2.68 (m, 1H), 2.62 - 2.55 (m, 2H), 2.39 - 2.33 (m, 1H), 1.17 - 0.93 (m, 7H), 0.77 - 0.67 (m, 2H); LCMS (Method G): Rt = 1.56 min, m/z = 604.2 $[M+H]^+$; HPLC (Method G): Rt = 4.65 min, 98.42%; Chiral SFC (Method AX): Rt = 9.14 min, 100%.

Example 422. (*E1*)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 422)



Step 1. (E1)-1-Oxa-7-azaspiro[4.4]nonane (Isomer 1) and (E2)-1-oxa-7-azaspiro[4.4]nonane (Isomer 2)



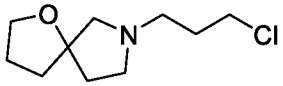
Isomer 1 Isomer 2

(±)-1-Oxa-7-azaspiro[4.4]nonane hydrochloride (1.2 g, 7.33 mmol) was purified by chiral Prep SFC (Method AS). The fractions were concentrated under reduced pressure and lyophilized to obtain (*E1*)-1-oxa-7-azaspiro[4.4]nonane (0.4 g, 42.7% yield) and (*E2*)-1-oxa-7-azaspiro[4.4]nonane (0.4 g, 40.5% yield) as liquids.

Isomer 1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 - 3.81 (m, 2H), 3.43 - 3.36 (m, 2H), 3.28 (br d, *J* = 11.9 Hz, 1H), 3.09 (br d, *J* = 11.9 Hz, 1H), 2.13 - 1.88 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 0.52 min, m/z = 128.1 $[M+H]^+$, 99.58%; Chiral SFC (Method AAX): Rt = 3.52 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 - 3.78 (m, 2H), 3.36 - 3.23 (m, 2H), 3.19 (dd, *J* = 1.3, 11.9 Hz, 1H), 2.96 (d, *J* = 11.9 Hz, 1H), 2.09 - 1.84 (m, 6H), one proton merged with solvent peaks; LCMS (Method L): Rt = 0.37 min, m/z = 492.2 $[M+H]^+$, 94.38%; Chiral SFC (Method AAX): Rt = 5.16 min, 100%.

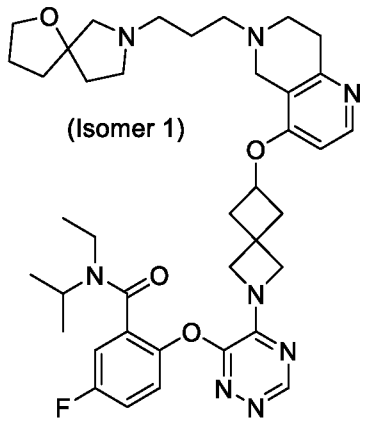
Step 2. (E1)-7-(3-Chloropropyl)-1-oxa-7-azaspiro[4.4]nonane



This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.9 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of (*E1*)-1-oxa-7-azaspiro[4.4]nonane was used. The reaction was stirred in a pressure vial. After work-up, the filtrate was concentrated under reduced pressure to afford crude (*E1*)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane as a liquid. This material was used without further purification.

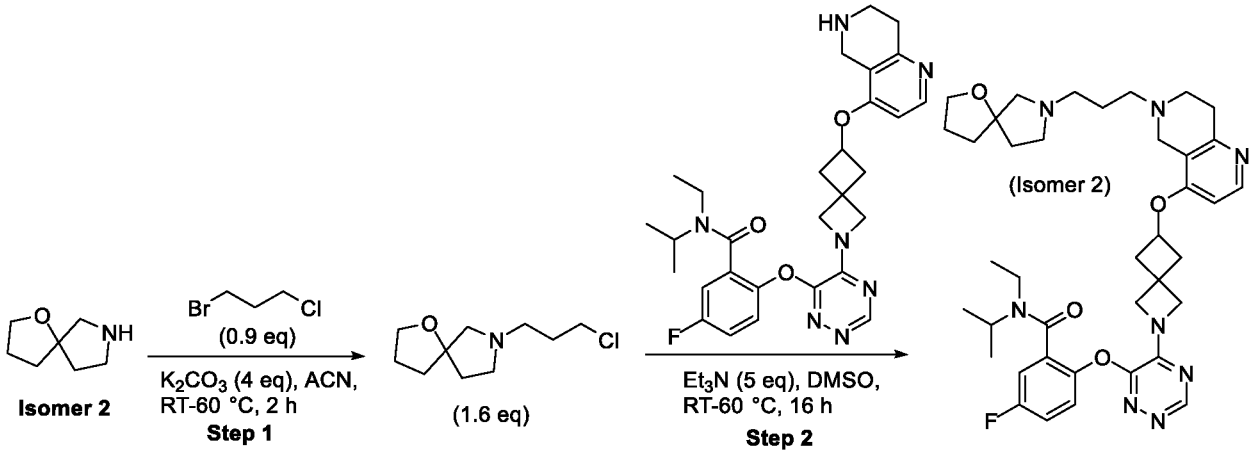
Yield: 46.8%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 - 3.79 (m, 2H), 3.62 (t, *J* = 6.6 Hz, 1H), 2.78 - 2.47 (m, 6H), 2.06 - 1.81 (m, 9H).

Step 3. (E1)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

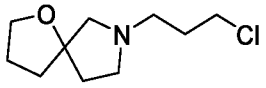


In an 8 mL pressure vial under a nitrogen atmosphere, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (100 mg, 0.183 mmol) and (*E1*)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane (59.5 mg, 0.292 mmol) were dissolved in DMSO (2 mL). To this solution, TEA (0.127 mL, 0.913 mmol) was added at RT. The reaction was stirred at 60 °C for 16 h. The reaction progress was monitored by TLC (20% MeOH in DCM). The reaction was diluted with water (10 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford (*E1*)-2-((5-(6-((6-(3-(1-oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (23 mg, 17.60% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 6.69 (d, J = 5.7 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.67 - 4.48 (m, 2H), 4.33 - 4.11 (m, 2H), 3.71 - 3.59 (m, 3H), 3.47 - 3.40 (m, 3H), 3.18 - 2.98 (m, 2H), 2.86 - 2.77 (m, 4H), 2.70 - 2.67 (m, 2H), 2.47 - 2.37 (m, 4H), 1.88 - 1.59 (m, 9H), 1.17 - 0.62 (m, 9H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.69 min, m/z = 715.3 $[M+H]^+$; HPLC (Method G): Rt = 4.89 min, 96.96%; Chiral SFC (Method AAY): Rt = 2.61 min, 100%.

Example 423. (*E2*)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 423)



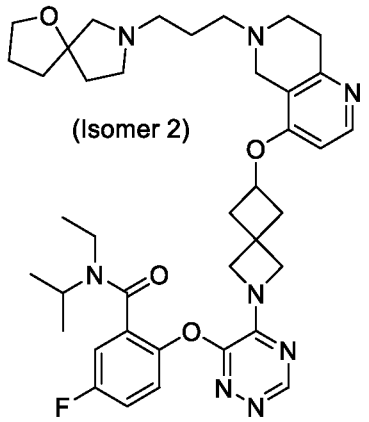
Step 1. (E2)-7-(3-Chloropropyl)-1-oxa-7-azaspiro[4.4]nonane



This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.9 equivalent of 1-bromo-3-chloropropane, except that 1 equivalent of (*E2*)-1-oxa-7-azaspiro[4.4]nonane was used. The reaction was stirred in a pressure vial. After work-up, the filtrate was concentrated under reduced pressure to afford crude (*E2*)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane as a liquid. This material was used without further purification.

Yield: 64.0%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 - 3.79 (m, 2H), 3.63 (t, *J* = 6.6 Hz, 1H), 2.94 - 2.55 (m, 6H), 2.10 - 1.79 (m, 9H).

Step 2. (E2)-2-((5-(6-((6-(3-(1-Oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

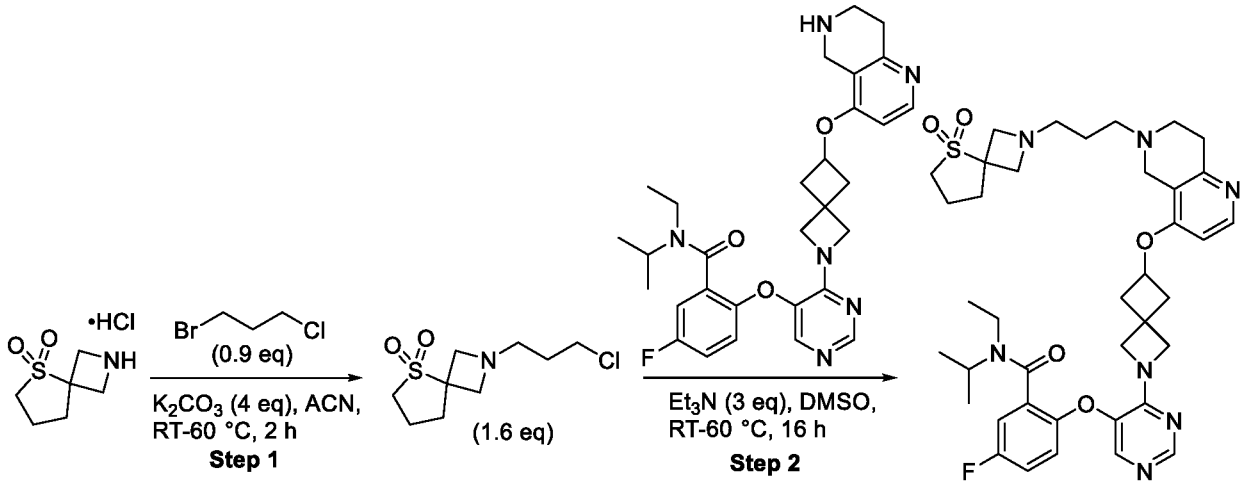


This compound was synthesized following the procedure described for the synthesis of Example 422, step 3, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-

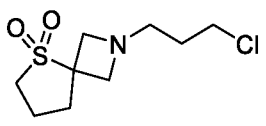
((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 1.6 equivalents of (*E2*)-7-(3-chloropropyl)-1-oxa-7-azaspiro[4.4]nonane was used. The reaction was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AR). The fractions were concentrated under reduced pressure and lyophilized to afford (*E2*)-2-((5-(6-((6-(3-(1-oxa-7-azaspiro[4.4]nonan-7-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 22.65%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.39 - 7.31 (m, 2H), 6.69 (d, *J* = 5.6 Hz, 1H), 4.79 (quin, *J* = 6.6 Hz, 1H), 4.67 - 4.49 (m, 2H), 4.33 - 4.10 (m, 2H), 3.72 - 3.55 (m, 3H), 3.43 - 3.38 (m, 3H), 3.16 - 2.99 (m, 2H), 2.87 - 2.77 (m, 4H), 2.69 - 2.64 (m, 2H), 2.45 - 2.35 (m, 4H), 1.87 - 1.59 (m, 9H), 1.17 - 0.67 (m, 9H), four protons merged with solvent peaks; LCMS (Method G): Rt = 1.70 min, m/z = 715.3 $[M+H]^+$; HPLC (Method G): Rt = 4.89 min, 98.58%; Chiral SFC (Method AAZ): Rt = 4.13 min, 100%.

Example 424. 2-((4-(6-((6-(3-(5,5-Dioxido-5-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 424)



Step 1. 2-(3-Chloropropyl)-5-thia-2-azaspiro[3.4]octane 5,5-dioxide

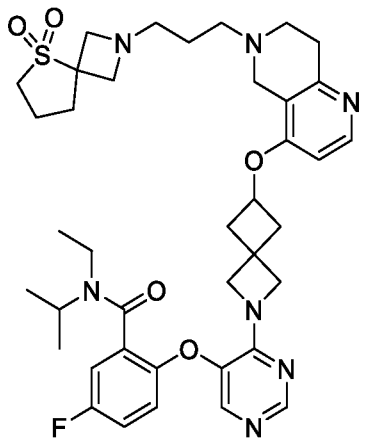


This compound was synthesized following the procedure described for the synthesis of Intermediate 53, starting with 0.9 equivalent of 1-bromo-3-chloropropane, except that 1

equivalent of 5-thia-2-azaspiro[3.4]octane 5,5-dioxide was used. After work-up, the filtrate was concentrated under reduced pressure to afford crude 2-(3-chloropropyl)-5-thia-2-azaspiro[3.4]octane 5,5-dioxide as a liquid. This material was used without further purification.

Yield: 63.6%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 - 3.63 (m, 2H), 3.62 - 3.57 (m, 2H), 3.28 (d, *J* = 8.9 Hz, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.65 (t, *J* = 6.9 Hz, 2H), 2.44 (t, *J* = 6.6 Hz, 2H), 2.12 - 2.03 (m, 2H), 1.84 (quin, *J* = 6.7 Hz, 2H).

Step 2. 2-((4-(6-((6-(3-(5,5-Dioxido-5-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

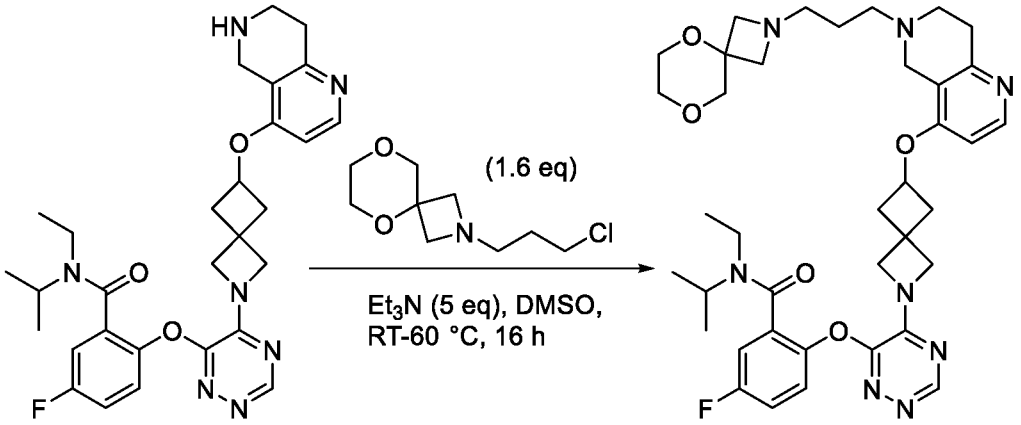


This compound was synthesized following the procedure described for the synthesis Example 422, step 3, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and 1.6 equivalents of 2-(3-chloropropyl)-5-thia-2-azaspiro[3.4]octane 5,5-dioxide.except that 3 equivalents of Et_3N was used. After work-up, the crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AR) The fractions were concentrated under reduced pressure and lyophilized to afford 2-((4-(6-((6-(3-(5,5-dioxido-5-thia-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 7.12%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.21 - 8.14 (m, 1H), 7.76 - 7.65 (m, 1H), 7.34 - 7.22 (m, 2H), 7.11 - 7.00 (m, 1H), 6.69 - 6.63 (m, 1H), 4.79 - 4.69 (m, 1H), 4.47 - 4.06 (m, 4H), 3.81 - 3.69 (m, 1H), 3.44 - 3.38 (m, 4H), 3.28 - 3.19 (m, 2H), 3.14 (d, *J* = 8.3 Hz, 2H), 3.05 (t, *J* = 7.4 Hz, 2H), 2.83 - 2.74 (m, 4H), 2.69 - 2.63 (m, 2H),

2.48 - 2.44 (m, 2H), 2.42 (br t, J = 7.1 Hz, 2H), 2.31 - 2.22 (m, 4H), 1.91 (quin, J = 7.0 Hz, 2H), 1.51 (quin, J = 7.0 Hz, 2H), 1.23 - 0.97 (m, 9H); LCMS (Method L): Rt = 1.58 min, m/z = 748.6 $[M+H]^+$; HPLC (Method G): Rt = 4.87 min, 99.77%.

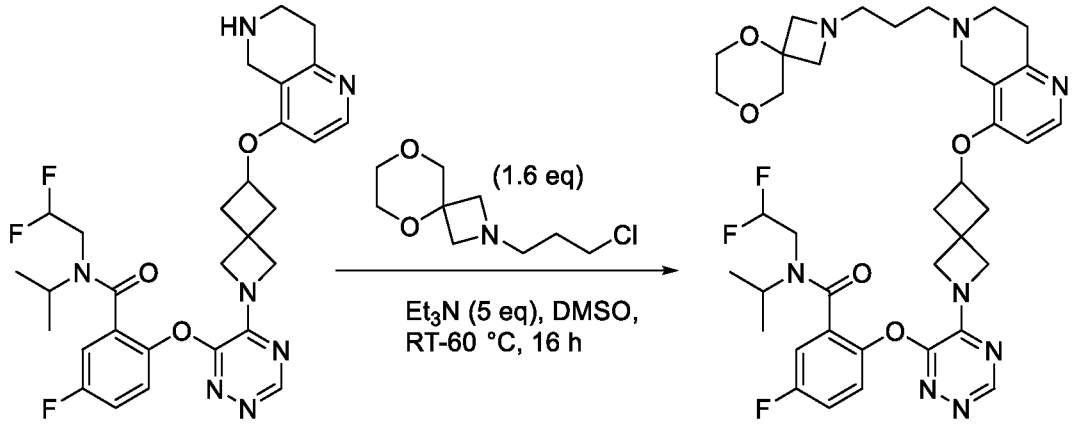
Example 425. 2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 425)



This compound was synthesized following the procedure described for the synthesis of Example 422, step 3, starting with 1 equivalent of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide, except that 1.6 equivalents of 2-(3-chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane was used. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AM). The fractions were concentrated under reduced pressure and lyophilized to afford 2-((5-(6-((6-(3-(5,8-dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide as a solid.

Yield: 23.48%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.40 - 7.30 (m, 2H), 6.68 (d, J = 5.7 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.69 - 4.45 (m, 2H), 4.32 - 4.10 (m, 2H), 3.68 - 3.57 (m, 3H), 3.53 (s, 4H), 3.40 (s, 2H), 3.29 - 3.25 (m, 2H), 3.18 - 2.99 (m, 2H), 2.89 - 2.71 (m, 7H), 2.70 - 2.65 (m, 2H), 2.47 - 2.34 (m, 4H), 2.33 – 2.25 (m, 1H), 1.52 (br s, 2H), 1.19 - 0.66 (m, 9H); LCMS (Method F): Rt = 1.78 min, m/z = 717.6 $[M+H]^+$; HPLC (Method G): Rt = 4.69 min, 99.15%.

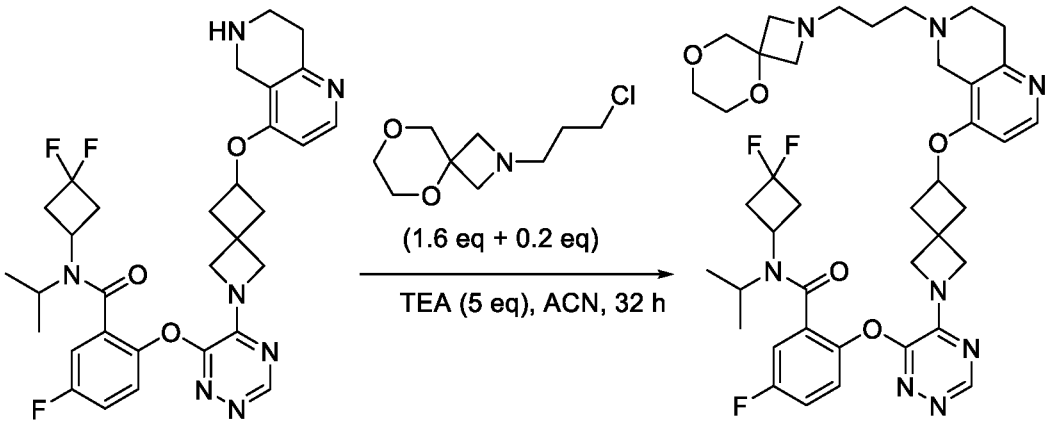
Example 426. 2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 426)



This compound was synthesized following the procedure described for the synthesis of Example 422, step 3, starting with 1 equivalent of *N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (0.1 g, 0.171 mmol) and 1.6 equivalents of 2-(3-chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane. After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method B). The fractions were concentrated under reduced pressure and lyophilized to afford 2-((5-(6-((6-(3-(5,8-dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2-difluoroethyl)-5-fluoro-*N*-isopropylbenzamide as a solid.

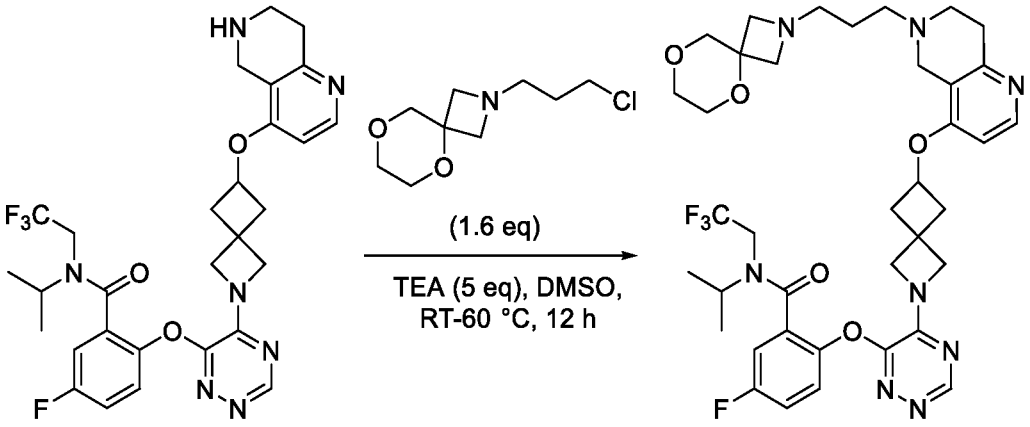
Yield: 13.18%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.38 (m, 2H), 6.69 (d, J = 5.6 Hz, 1H), 6.39 - 5.93 (m, 1H), 4.83 - 4.72 (m, 1H), 4.65 - 4.43 (m, 2H), 4.28 - 4.11 (m, 2H), 3.79 - 3.69 (m, 1H), 3.61 (s, 2H), 3.53 (s, 4H), 3.40 (s, 2H), 3.30 - 3.26 (m, 2H), 2.88 - 2.71 (m, 7H), 2.67 - 2.59 (m, 2H), 2.47 - 2.34 (m, 4H), 2.33 – 2.24 (m, 1H), 1.60 - 1.46 (m, 2H), 1.18 - 0.66 (m, 6H), two protons merged with solvent peaks; LCMS (Method L): Rt = 1.81 min, m/z = 753.4 $[M+H]^+$; HPLC (Method G): Rt = 4.90 min, 97.52%.

Example 427. 2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 427)



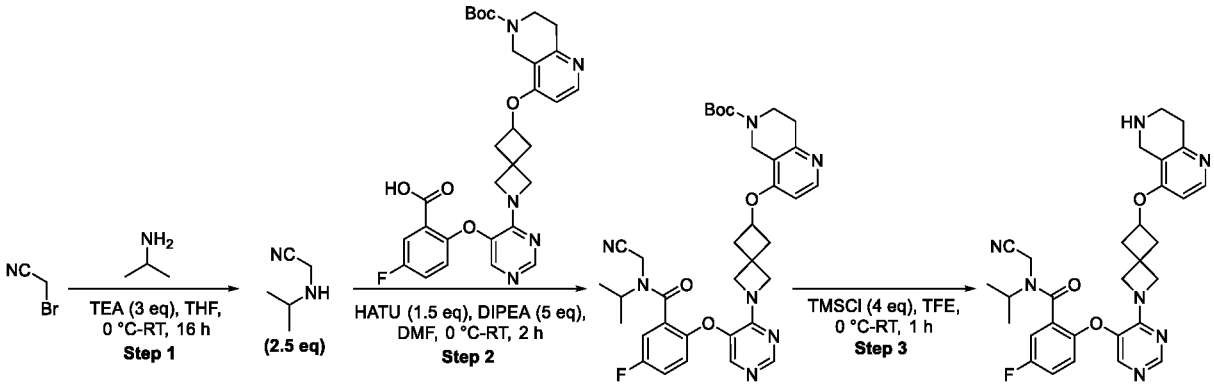
In a 4 mL pressure vial, *N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (120 mg, 0.197 mmol) and 2-(3-chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane (64.8 mg, 0.315 mmol) were added in DMSO (0.8 mL). To this reaction mixture, TEA (0.137 mL, 0.984 mmol) was added at RT and the reaction was stirred at 60 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The starting material was not consumed. Therefore, another lot of 2-(3-chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane (8.10 mg, 0.039 mmol, in 0.2 mL DMSO) was added at RT, and the reaction was stirred at 60 °C for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction mixture was concentrated under reduced pressure. The crude compound was purified by Prep HPLC (Method T) to obtain 2-((5-(6-((6-(3-(5,8-dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(3,3-difluorocyclobutyl)-5-fluoro-*N*-isopropylbenzamide (37 mg, 24.01% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.51 - 7.43 (m, 1H), 7.42 - 7.35 (m, 2H), 6.67 (br s, 1H), 4.79 (quin, J = 6.4 Hz, 1H), 4.68 - 4.51 (m, 2H), 4.33 - 4.10 (m, 2H), 3.91 - 3.80 (m, 1H), 3.67 - 3.58 (m, 3H), 3.53 (s, 4H), 3.40 (br s, 2H), 3.31 - 3.23 (m, 3H), 2.89 - 2.61 (m, 11H), 2.46 - 2.39 (m, 3H), 2.33 - 2.27 (m, 1H), 1.59 - 1.37 (m, 2H), 1.21 - 0.64 (m, 6H), two protons merged with solvent peaks; LCMS (Method L): Rt = 1.84 min, m/z = 779.5 $[M+H]^+$; HPLC (Method G): Rt = 5.24 min, 98.25%.

Example 428. 2-((5-(6-((6-(3-(5,8-Dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (Compound No. 428)

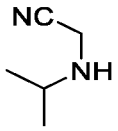


This compound was synthesized following the procedure described for the synthesis of Example 422, step 3, starting with 1 equivalent of 5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(2,2,2-trifluoroethyl)benzamide (140 mg, 0.233 mmol) and 1.6 equivalents of 2-(3-chloropropyl)-5,8-dioxa-2-azaspiro[3.5]nonane. The crude was purified by Prep-HPLC (Method V) to obtain 2-((5-(6-((6-(3-(5,8-dioxa-2-azaspiro[3.5]nonan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)benzamide (60 mg, 33.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.53 - 7.38 (m, 3H), 6.68 (br d, J = 3.9 Hz, 1H), 4.78 (quin, J = 6.6 Hz, 1H), 4.68 - 4.44 (m, 2H), 4.38 - 3.97 (m, 4H), 3.84 - 3.72 (m, 1H), 3.61 (s, 2H), 3.53 (s, 4H), 3.44 – 3.37 (m, 2H), 3.31 – 3.25 (m, 2H), 2.87 - 2.62 (m, 9H), 2.48 - 2.41 (m, 4H), 2.32 - 2.23 (m, 1H), 1.60 - 1.42 (m, 2H), 1.22 - 0.59 (m, 6H); LCMS (Method F): Rt = 1.86 min, m/z = 771.5 $[M+H]^+$; HPLC (Method G): Rt = 5.03 min, 99.57%.

Example 429. *N*-(Cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound N0. 429)

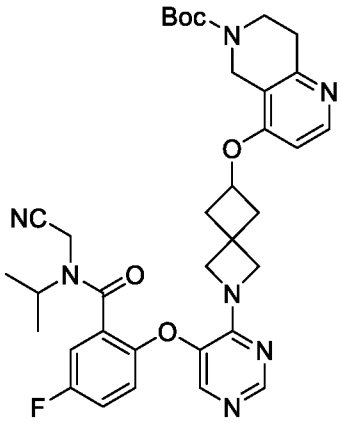


Step 1. 2-(Isopropylamino)acetonitrile



To a stirred solution of 2-bromoacetonitrile (2.59 mL, 37.2 mmol) in THF (40 mL), TEA (14.15 mL, 102 mmol) and propan-2-amine (2.0 g, 33.8 mmol) were added at 0 °C under a nitrogen atmosphere. The reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10 % MeOH in DCM). After completion, the reaction was quenched with water (20 mL) and the mixture was extracted with EtOAc (100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain crude 2-(isopropylamino)acetonitrile (3.0 g, 90% yield). This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.59 (br s, 2H), 2.81 (spt, J = 6.2 Hz, 1H), 2.49 - 2.42 (m, 1H), 0.97 (d, J = 6.1 Hz, 6H).

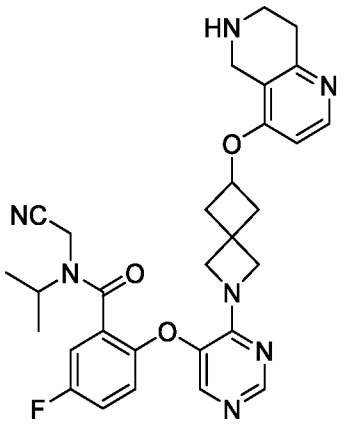
Step 2. tert-Butyl 4-((2-(5-(2-((cyanomethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl and 2.5 equivalents of 2-(isopropylamino)acetonitrile, except that 5 equivalents of DIPEA was used. After completion, the reaction was concentrated under reduced pressure and EtOAc was added to the residue. The organic layer was washed with ice-cold water, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 8-9% MeOH in DCM) to obtain *tert*-butyl 4-((2-(5-(2-((cyanomethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 71.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.23 (d, J = 5.6 Hz, 1H), 7.84 (s, 1H), 7.41 - 7.28 (m, 2H), 7.06 (dd, J = 4.3, 9.1 Hz, 1H), 6.73 (d, J = 5.8 Hz, 1H), 4.83 - 4.69 (m, 1H), 4.46 (s, 2H), 4.37 (s, 2H), 4.32 - 4.06 (m, 4H), 3.95 - 3.84 (m, 1H), 3.62 (br t, J = 5.9 Hz, 2H), 2.85 - 2.75 (m, 4H), 2.31 - 2.21 (m, 2H), 1.51 - 1.40 (m, 9H), 1.18 - 1.07 (m, 6H); LCMS (Method G): Rt = 1.93 min, m/z = 658.4 $[M+H]^+$, 92.90%.

Step 3. N-(Cyanomethyl)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



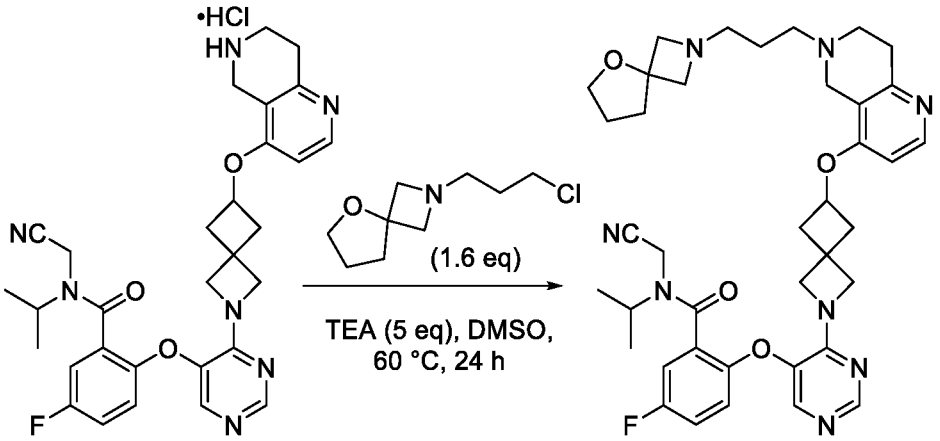
This reaction was performed following the same procedure in two batches (80 mg and 350 mg).

This compound was synthesized following the procedure described for the synthesis of Example 9, step 4, starting with *tert*-butyl 4-((2-(5-(2-((cyanomethyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, except that 4 equivalents of TMSCl was used and 2,2,2-trifluoroethanol was used as a solvent. The reaction was concentrated under reduced pressure and the residue was triturated with EtOAc to obtain crude *N*-(cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride. The crude was purified by Prep HPLC (Method N) to afford *N*-(cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Combined yield: 16.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.85 (s, 1H), 7.38 (dd, J = 3.1, 8.1 Hz, 1H), 7.35 - 7.28 (m, 1H), 7.05 (dd, J = 4.3, 9.1 Hz, 1H), 6.63 (d, J = 5.6 Hz, 1H), 4.70 (quin, J = 6.7 Hz, 1H), 4.50 - 4.43 (m, 2H), 4.30 - 4.05 (m, 4H), 3.89 (quin, J = 6.5 Hz, 1H), 3.69 (s, 2H), 2.95 (t, J = 5.8 Hz, 2H), 2.82 - 2.72 (m, 2H), 2.68 (br t, J = 5.5 Hz, 2H), 2.28 – 2.16 (m, 2H), 1.20 - 1.04 (m, 6H), one proton

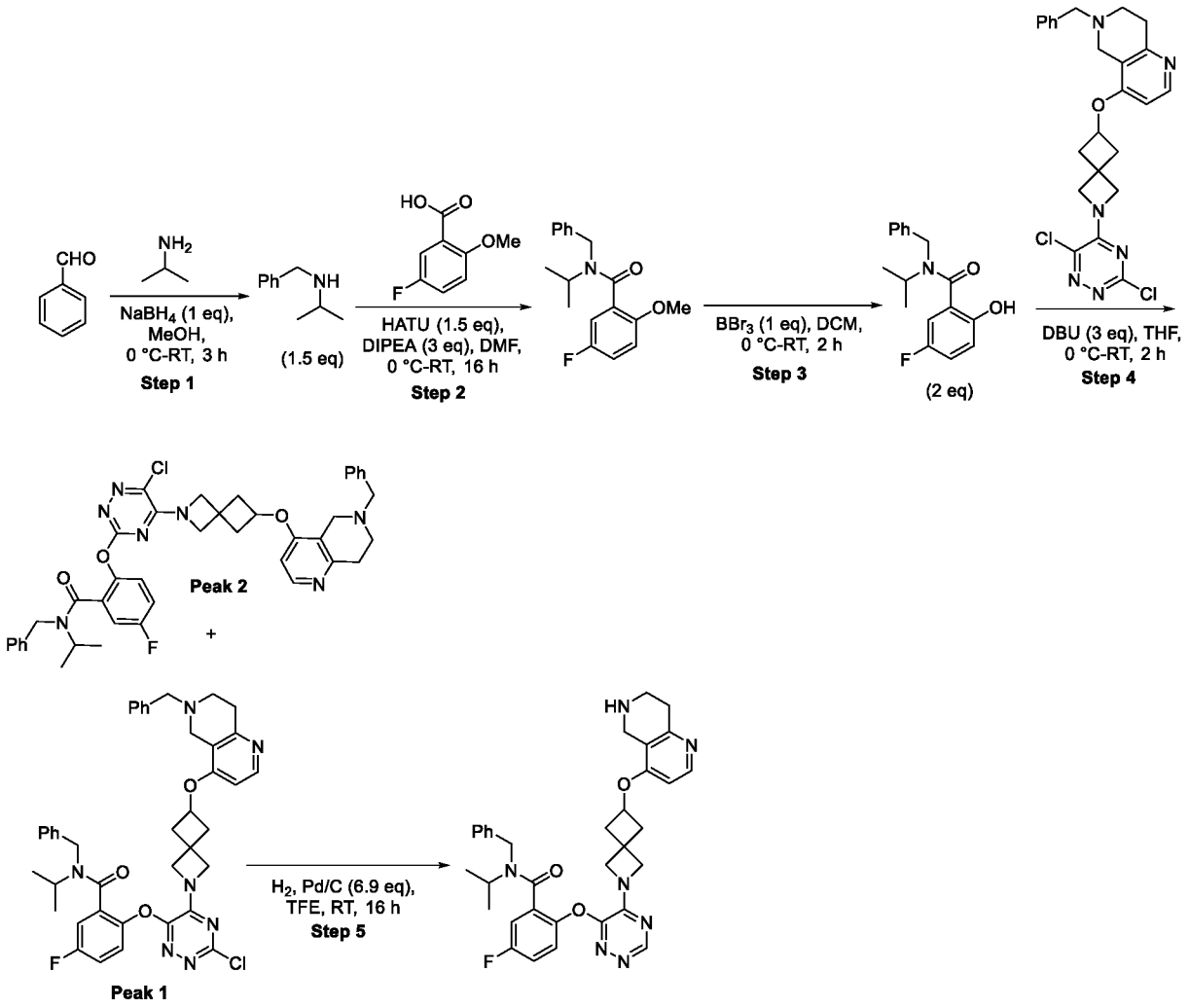
merged with solvent peaks; LCMS (Method G): Rt = 1.42 min, m/z = 558.1 $[M+H]^+$; HPLC (Method G): Rt = 4.30 min, 99.61%.

Example 430. 2-((4-(6-(((6-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(cyanomethyl)-5-fluoro-*N*-isopropylbenzamide (Compound No. 430)

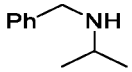


This compound was synthesized following the procedure described for the synthesis of Example 422, step 3, starting with 1 equivalent of *N*-(cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 1.6 equivalents of 2-(3-chloropropyl)-5-oxa-2-azaspiro[3.4]octane. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-(((6-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(cyanomethyl)-5-fluoro-*N*-isopropylbenzamide as a solid. Yield: 23.29%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s, 1H), 8.17 (d, *J* = 5.8 Hz, 1H), 7.85 (s, 1H), 7.38 (dd, *J* = 3.1, 8.1 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.05 (dd, *J* = 4.3, 9.1 Hz, 1H), 6.64 (d, *J* = 5.6 Hz, 1H), 4.77 - 4.67 (m, 1H), 4.46 (d, *J* = 1.8 Hz, 2H), 4.30 - 4.03 (m, 4H), 3.95 - 3.83 (m, 1H), 3.65 (t, *J* = 6.8 Hz, 2H), 3.39 (s, 2H), 3.27 - 3.22 (m, 2H), 2.91 - 2.86 (m, 2H), 2.83 - 2.73 (m, 4H), 2.70 - 2.63 (m, 2H), 2.48 - 2.44 (m, 2H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.30 - 2.19 (m, 2H), 2.02 - 1.94 (m, 2H), 1.86 - 1.75 (m, 2H), 1.50 (quin, *J* = 7.1 Hz, 2H), 1.20 - 1.01 (m, 6H); LCMS (Method G): Rt = 1.59 min, m/z = 711.2 $[M+H]^+$; HPLC (Method G): Rt = 4.81 min, 97.46%.

Example 431. *N*-Benzyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 431)

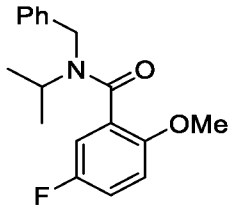


Step 1. N-Benzylpropan-2-amine



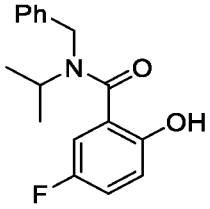
In a dried, 100 mL two neck round bottom flask under a nitrogen atmosphere, propan-2-amine (14.41 mL, 169 mmol) and benzaldehyde (17.26 mL, 169 mmol) were added in MeOH (20 mL). To this solution, $NaBH_4$ (6.40 g, 169 mmol) was added at 0 °C and the reaction was stirred at RT for 3 h. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was concentrated under reduced pressure. EtOAc (100 mL) was added to the crude and the mixture was washed with saturated $NaHCO_3$ solution (3 x 50 mL). The combined organic layer was concentrated under reduced pressure to obtain crude *N*-benzylpropan-2-amine (20 g, 79% yield) as a liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 - 7.26 (m, 5H), 3.69 (s, 2H), 2.70 (spt, J = 6.2 Hz, 1H), 1.00 (d, J = 6.3 Hz, 6H), one proton merged with solvent peaks.

Step 2. N-Benzyl-5-fluoro-N-isopropyl-2-methoxybenzamide



In a dried, 250 mL two neck round bottom flask under a nitrogen atmosphere, 5-fluoro-2-methoxybenzoic acid (5 g, 29.4 mmol) was added in DMF (50 mL). To this solution, *N*-benzylpropan-2-amine (6.58 g, 44.1 mmol), HATU (16.76 g, 44.1 mmol), and DIPEA (15.40 mL, 88 mmol) were added at RT. The reaction was stirred for 16 h at the same temperature. The reaction progress was monitored by TLC (50% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (100 mL), and the mixture was extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with brine solution (3 x 50 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using EtOAc in hexane (product was eluted at 35% EtOAc in hexane) to obtain *N*-benzyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide (8 g, 89% yield) as a solid. LCMS (Method G): Rt = 2.07 min, m/z = 302.4 $[M+H]^+$, 89.37%.

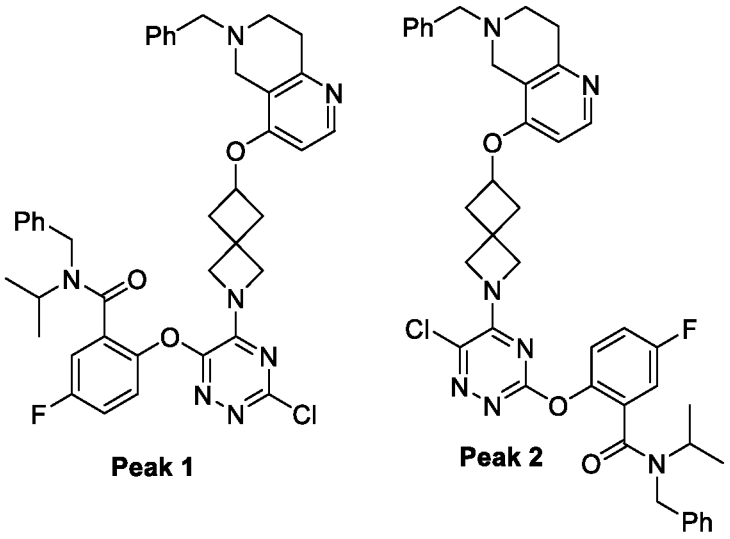
Step 3. N-Benzyl-5-fluoro-2-hydroxy-N-isopropylbenzamide



In a dried, 100 mL two neck round bottom flask under a nitrogen atmosphere, *N*-benzyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide (500 mg, 1.659 mmol) was added in DCM (10 mL). To this solution, BBr_3 (1.659 mL, 1.659 mmol, 1M in DCM) was added at 0 °C and the mixture was stirred at RT for 2 h. The reaction progress was monitored by TLC (30% EtOAc in hexane). After completion, the reaction was quenched with ice-cold water (20 mL), and the mixture was extracted with DCM (2 x 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (20 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude *N*-benzyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (450 mg, 71.7% yield) as a solid. This material was used without further purification. LCMS (Method L): Rt = 1.84 min, m/z = 288.1 $[M+H]^+$, 78.63%.

Step 4. N-Benzyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide and N-benzyl-2-((5-(6-

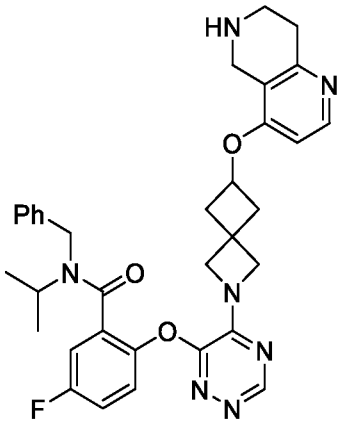
((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-6-chloro-1,2,4-triazin-3-yl)oxy)-5-fluoro-N-isopropylbenzamide



In a 50 mL two neck round bottom flask under a nitrogen atmosphere, 6-benzyl-4-((2-(3,6-dichloro-1,2,4-triazin-5-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,7,8-tetrahydro-1,6-naphthyridine (380 mg, 0.786 mmol) and *N*-benzyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (452 mg, 1.572 mmol) were added in THF (5 mL). To this mixture, DBU (0.352 mL, 2.358 mmol) was added at 0 °C and the reaction was stirred at 40 °C for 24 h. The reaction progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with EtOAc (2 x 20 mL). The filtrate was concentrated under reduced pressure and the crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 45% MeOH in DCM) to obtain *N*-benzyl-2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (430 mg, 69.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 - 8.14 (m, 1H), 7.54 - 7.12 (m, 13H), 6.74 - 6.61 (m, 1H), 4.93 - 4.61 (m, 3H), 4.56 - 4.49 (m, 1H), 4.39 - 4.23 (m, 2H), 3.92 - 3.81 (m, 1H), 3.75 - 3.60 (m, 2H), 3.56 - 3.41 (m, 2H), 2.86 - 2.66 (m, 6H), 2.33 - 2.19 (m, 2H), 1.23 - 0.65 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.39 min, m/z = 735.3 $[M+H]^+$, 93.53%.

Note: Peak 2 was not isolated.

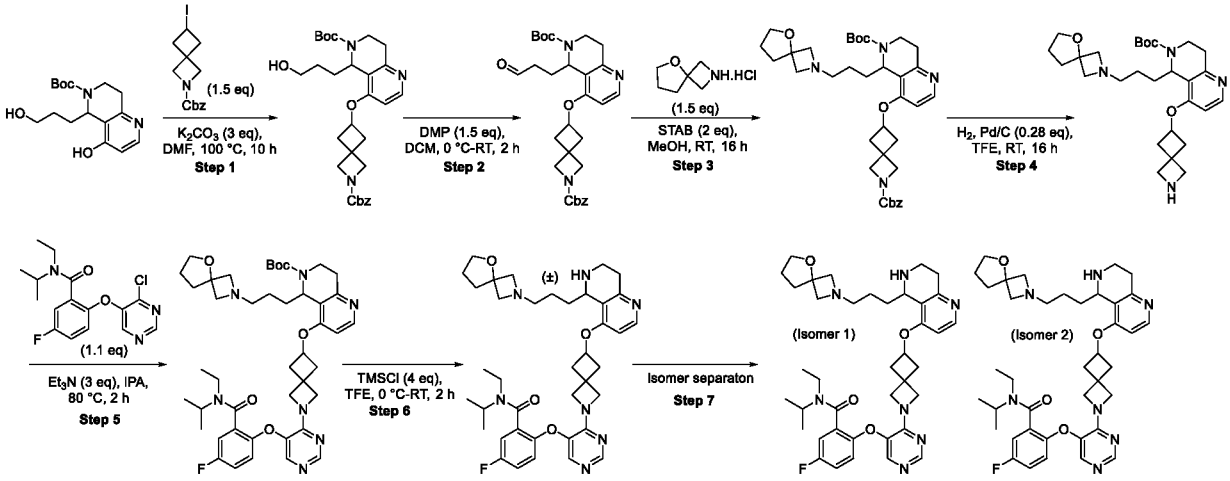
Step 5. N-Benzyl-5-fluoro-N-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide



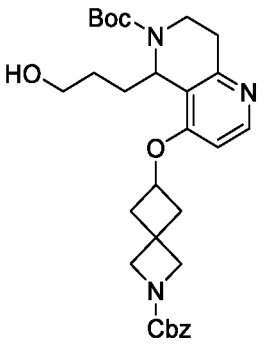
In a 25 mL round bottom flask *N*-benzyl-2-((5-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (310 mg, 0.422 mmol) was added in TFE (8 mL). To this solution, Pd-C (310 mg, 2.91 mmol) was added and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by achiral Prep SFC (Method T) to obtain the desired product (110 mg; LCMS purity: 94.8%). An impurity was observed in the ^{1}HNMR spectrum. Therefore, 80 mg was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-benzyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (35.81 mg, 44.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (br s, 1H), 8.23 - 8.10 (m, 1H), 7.56 - 7.35 (m, 3H), 7.33 - 7.09 (m, 5H), 6.66 (br d, J = 12.9 Hz, 1H), 4.92 - 4.70 (m, 2H), 4.68 - 4.38 (m, 2H), 4.36 - 4.16 (m, 3H), 3.98 - 3.83 (m, 1H), 3.79 - 3.63 (m, 2H), 2.98 (br d, J = 4.2 Hz, 2H), 2.90 - 2.60 (m, 5H), 2.34 - 2.17 (m, 2H), 1.20 - 0.56 (m, 6H); LCMS (Method F): Rt = 1.69 min, m/z = 610.4 $[M+H]^+$; HPLC (Method G): Rt = 4.90 min, 99.29%.

Example 432. (*E1*)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 432)

Example 433. (*E2*)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 433)

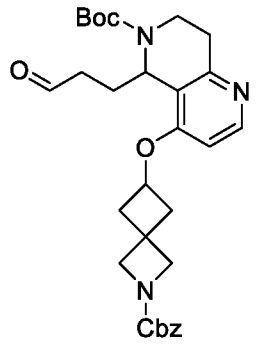


Step 1. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



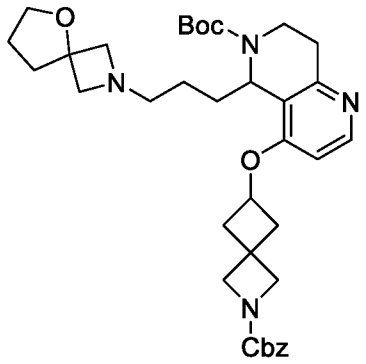
In a 500 mL two neck round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (7.5 g, 24.32 mmol) was added in DMF (100 mL). To this solution, K_2CO_3 (10.08 g, 73.0 mmol) and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (13.03 g, 36.5 mmol) were added at RT and the reaction was stirred at 100 °C for 10 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with EtOAc (100 mL) and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography using MeOH in DCM (product was eluted at 5% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (6.7 g, 51.1% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (br d, J = 5.4 Hz, 1H), 7.43 - 7.28 (m, 5H), 6.70 (d, J = 5.6 Hz, 1H), 5.21 - 5.05 (m, 1H), 5.03 (s, 2H), 4.86 - 4.66 (m, 1H), 4.46 - 4.32 (m, 1H), 4.21 - 3.84 (m, 5H), 3.60 - 3.39 (m, 2H), 3.29 - 3.18 (m, 1H), 2.83 - 2.69 (m, 4H), 2.36 - 2.21 (m, 2H), 1.86 - 1.72 (m, 1H), 1.66 - 1.44 (m, 3H), 1.41 (s, 9H); LCMS (Method G): Rt = 1.96 min, m/z = 538.4 $[M+H]^+$, 99.73%.

Step 2. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-oxopropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



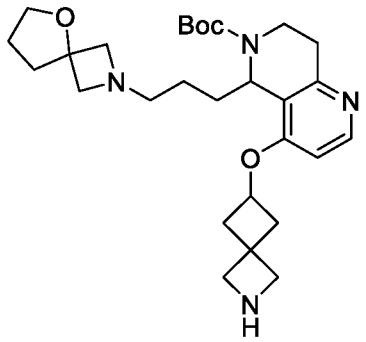
In a dried, 100 mL two neck round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.5 g, 2.79 mmol) was added in DCM (10 mL). To this solution, Dess-Martin periodinane (1.775 g, 4.18 mmol) was added at 0 °C and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (100% EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with DCM (2 x 20 mL). The filtrate was washed with saturated $NaHCO_3$ solution (20 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-oxopropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.2 g, 63.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.83 - 9.61 (m, 1H), 8.25 (d, J = 5.5 Hz, 1H), 7.45 - 7.26 (m, 5H), 6.73 (d, J = 5.7 Hz, 1H), 5.21 - 5.06 (m, 1H), 4.89 - 4.72 (m, 1H), 4.23 - 3.80 (m, 5H), 3.28 - 3.12 (m, 1H), 2.84 - 2.69 (m, 4H), 2.39 - 2.23 (m, 3H), 2.19 - 2.05 (m, 1H), 1.95 - 1.81 (m, 1H), 1.52 - 1.31 (m, 11H), one proton merged with solvent peaks; LCMS (Method L): Rt = 2.14 min, m/z = 536.3 $[M+H]^+$, 79.54%.

Step 3. (±)-tert-Butyl 5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



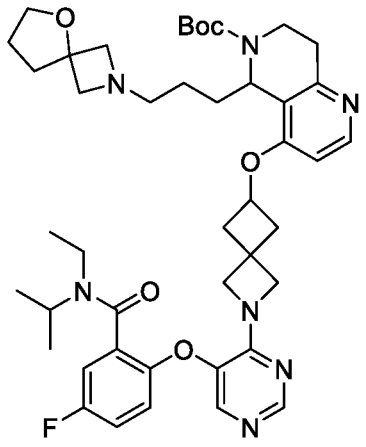
To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-oxopropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.2 g, 2.240 mmol) in MeOH (10 mL), 5-oxa-2-azaspiro[3.4]octane hydrochloride (0.503 g, 3.36 mmol) was added at RT. The reaction was stirred at RT for 30 min. To this reaction mixture, sodium triacetoxyborohydride (0.950 g, 4.48 mmol) was added at 0 °C and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with saturated $NaHCO_3$ (50 mL) and the mixture was extracted with 10% MeOH in DCM (2 x 50 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (750 mg, 49.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (br d, J = 5.4 Hz, 1H), 7.43 - 7.28 (m, 5H), 6.70 (d, J = 5.6 Hz, 1H), 5.19 - 5.05 (m, 1H), 5.03 (s, 2H), 4.83 - 4.72 (m, 1H), 4.18 - 3.87 (m, 5H), 3.64 (br t, J = 6.6 Hz, 2H), 3.26 - 3.14 (m, 3H), 2.92 - 2.85 (m, 2H), 2.84 - 2.70 (m, 4H), 2.44 - 2.37 (m, 1H), 2.32 - 2.17 (m, 2H), 2.01 - 1.92 (m, 2H), 1.84 - 1.70 (m, 3H), 1.66 - 1.51 (m, 1H), 1.41 (s, 9H), 1.35 - 1.21 (m, 2H), one proton merged with solvent peaks; LCMS (Method L): Rt = 2.13 min, m/z = 633.9 $[M+H]^+$, 94.15%.

Step 4. (±)-tert-Butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 50 mL round bottom flask, (±)-*tert*-butyl 5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (170 mg, 0.269 mmol) was added in TFE (10 mL). To this solution, Pd-C (80 mg, 0.075 mmol) was added, and the reaction was stirred under a hydrogen atmosphere (balloon pressure) at RT for 18 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (120 mg, 57.3% yield) as a solid. This material was used without further purification. LCMS (Method L): Rt = 1.68 min, m/z = 499.5 $[M+H]^+$, 64.33%.

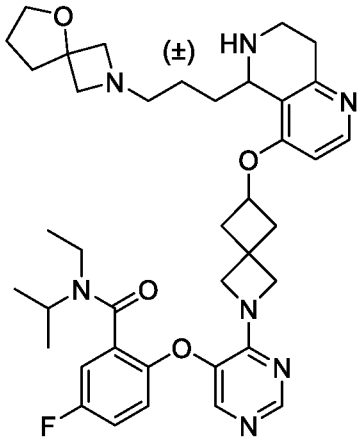
Step 5. (±)-tert-Butyl 5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-(2-azaspiro[3.4]octan-2-yl)propyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (460 mg, 0.926 mmol) in IPA (10 mL), TEA (0.387 mL, 2.78 mmol) and 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (344 mg, 1.019 mmol) were added at RT. The reaction was stirred at 80 °C for 2 h. The reaction progress was monitored by TLC (10%

MeOH in DCM). After completion, the reaction was quenched with water (40 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-*tert*-butyl 5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (570 mg, 56.9% yield) as a solid. LCMS (Method F): Rt = 2.55 min, m/z = 800.5 $[M+H]^+$, 72.03%.

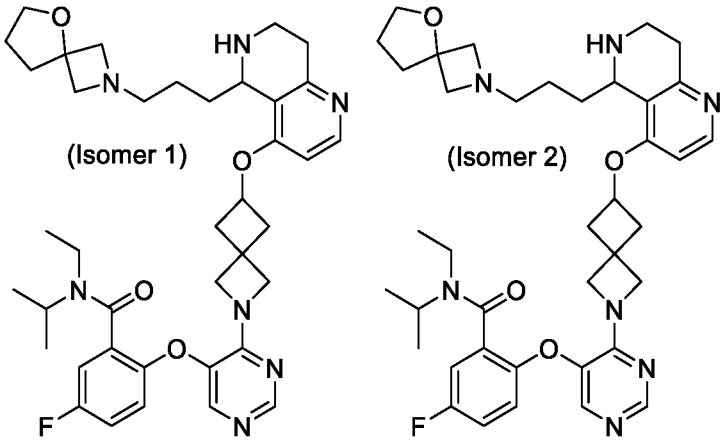
Step 6. (±)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



In a dried, 100 mL round bottom flask under a nitrogen atmosphere, (±)-*tert*-butyl 5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-4-((2-(5-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (570 mg, 0.513 mmol) was added in TFE (5 mL). To this solution, TMSCl (0.260 mL, 2.052 mmol) was added at 0 °C and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. To this residue, water (30 mL) was added and the mixture was extracted with 10% MeOH in DCM (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (±)-2-((4-(6-((5-(3-(5-

oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (245 mg, 66.9% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 7.77 - 7.64 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 - 7.01 (m, 1H), 6.63 (d, *J* = 5.6 Hz, 1H), 4.81 - 4.61 (m, 1H), 4.34 - 4.04 (m, 4H), 3.88 - 3.69 (m, 2H), 3.63 (t, *J* = 6.7 Hz, 2H), 3.46 - 3.37 (m, 1H), 3.28 - 3.11 (m, 3H), 3.05 - 2.94 (m, 1H), 2.92 - 2.74 (m, 5H), 2.71 - 2.60 (m, 2H), 2.45 - 2.31 (m, 2H), 2.29 - 2.16 (m, 2H), 1.98 - 1.93 (m, 2H), 1.77 (quin, *J* = 6.9 Hz, 2H), 1.63 - 1.31 (m, 4H), 1.23 - 0.97 (m, 9H), one proton merged with solvent peaks; LCMS (Method F): Rt = 1.76 min, m/z = 700.5 $[M+H]^+$; HPLC (Method G): Rt = 4.88 min, 98.77%; SFC (Method AL) = Peak 1: Rt = 6.68 min, 51.63%; Peak 2: Rt = 8.82 min, 46.73%.

Step 7. (E1)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and (E2)-2-((4-(6-((5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide

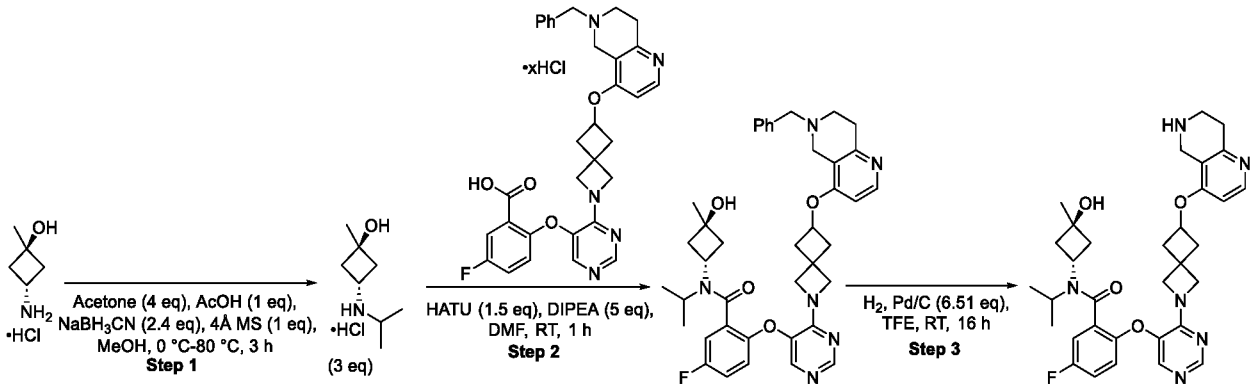


(±)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (245 mg) was purified by chiral Prep SFC (Method AT) to obtain both isomers, (*E1*)-2-((4-(6-((5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (83.17 mg, 33.9% yield) and (*E2*)-2-((4-(6-((5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (90 mg, 36.7% yield) as solids.

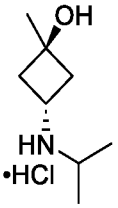
Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.24 (m, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.78 - 7.62 (m, 1H), 7.35 - 7.20 (m, 2H), 7.14 - 7.01 (m, 1H), 6.63 (br d, J = 5.7 Hz, 1H), 4.81 - 4.65 (m, 1H), 4.35 - 4.09 (m, 4H), 3.88 - 3.70 (m, 2H), 3.63 (t, J = 6.7 Hz, 2H), 3.43 - 3.38 (m, 1H), 3.24 - 3.11 (m, 3H), 3.06 - 2.95 (m, 1H), 2.93 - 2.75 (m, 5H), 2.72 - 2.59 (m, 2H), 2.43 - 2.32 (m, 2H), 2.29 - 2.16 (m, 2H), 2.00 - 1.93 (m, 2H), 1.77 (quin, J = 6.9 Hz, 2H), 1.62 - 1.34 (m, 4H), 1.26 - 0.95 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.73 min, m/z = 700.5 $[M+H]^+$; HPLC (Method G): Rt = 4.91 min, 99.83%; SFC (Method AL): Rt = 7.55 min, 99.63%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.76 - 7.63 (m, 1H), 7.35 - 7.21 (m, 2H), 7.14 - 7.01 (m, 1H), 6.63 (d, J = 5.6 Hz, 1H), 4.81 - 4.65 (m, 1H), 4.33 - 4.09 (m, 4H), 3.88 - 3.70 (m, 2H), 3.63 (t, J = 6.7 Hz, 2H), 3.45 - 3.37 (m, 1H), 3.26 - 3.15 (m, 3H), 3.04 - 2.95 (m, 1H), 2.93 - 2.75 (m, 5H), 2.71 - 2.60 (m, 2H), 2.42 - 2.33 (m, 2H), 2.28 - 2.18 (m, 2H), 2.01 - 1.91 (m, 2H), 1.77 (quin, J = 6.9 Hz, 2H), 1.63 - 1.35 (m, 4H), 1.24 - 0.94 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.84 min, m/z = 700.5 $[M+H]^+$; HPLC (Method G): Rt = 4.91 min, 99.79%. SFC (Method AL): Rt = 9.96 min, 100%.

Example 434. 5-Fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 434)



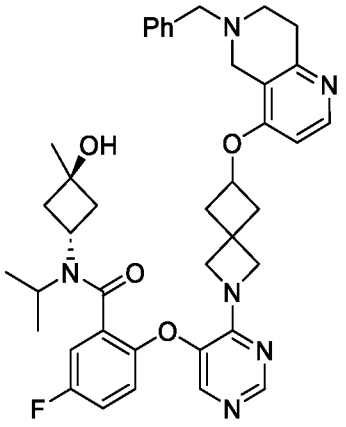
Step 1. (1r,3r)-3-(Isopropylamino)-1-methylcyclobutan-1-ol hydrochloride



To a stirred solution of (1*r*,3*r*)-3-amino-1-methylcyclobutan-1-ol hydrochloride (50 mg, 0.363 mmol) in MeOH (3 mL), acetone (0.108 mL, 1.453 mmol) and AcOH (0.0208 mL,

0.363 mmol) were added at 0 °C. The reaction was stirred RT for 20 min. To this mixture, 4 Å molecular sieves (50 mg, 0.363 mmol) and $NaBH_3CN$ (54.8 mg, 0.872 mmol) were added at 0 °C and the reaction was stirred at 80 °C for 3 h. The reaction progress was monitored by ^{1}H-NMR. After completion, the reaction was diluted with EtOAc (60 mL) and filtered through a Celite® pad, and the pad was washed with EtOAc (20 mL). The filtrate was acidified with 0.5 mL HCl (4M in 1,4 dioxane), and the mixture was concentrated under reduced pressure to obtain crude (1*r*,3*r*)-3-(isopropylamino)-1-methylcyclobutan-1-ol hydrochloride (50 mg, 77% yield) as a semi-solid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.43 (br s, 2H), 3.87 – 3.72 (m, 1H), 3.15 – 3.07 (m, 1H), 2.40 – 2.24 (m, 2H), 2.21 – 2.09 (m, 2H), 1.48 (s, 3H), 1.18 (d, J = 6.6 Hz, 6H), one proton merged with solvent peaks.

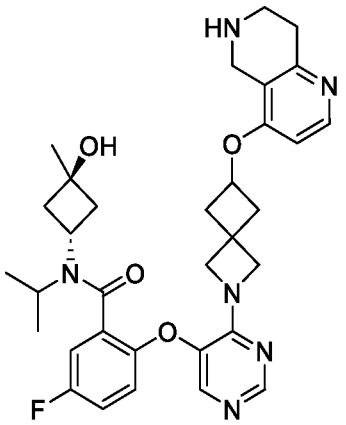
Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-((1r,3r)-3-hydroxy-3-methylcyclobutyl)-N-isopropylbenzamide



In a dried, 25 mL round bottom flask under a nitrogen atmosphere, 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl (500 mg, 0.881 mmol) and (1*r*,3*r*)-3-(isopropylamino)-1-methylcyclobutan-1-ol hydrochloride (475 mg, 2.64 mmol) were added in DMF (7 mL). To this mixture, DIPEA (0.769 mL, 4.40 mmol) and HATU (502 mg, 1.321 mmol) were added at 0 °C and the reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). Water (20 mL) was added to the reaction and the mixture was extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one

(Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropylbenzamide (360 mg, 57.1% yield) as a solid. LCMS (Method G): Rt = 1.93 min, m/z = 693.3 $[M+H]^+$, 96.80%.

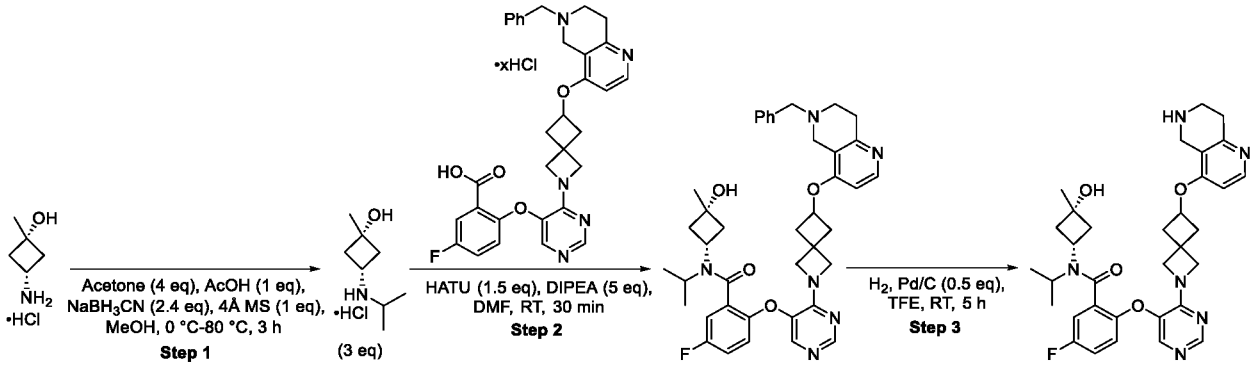
Step 3. 5-Fluoro-N-((1r,3r)-3-hydroxy-3-methylcyclobutyl)-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



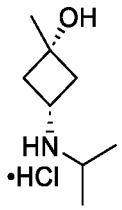
In a dried, 50 mL round bottom flask under a nitrogen atmosphere, 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropylbenzamide (200 mg, 0.289 mmol) was added in TFE (6 mL). Pd-C (200 mg, 1.879 mmol) was added to this solution, and the reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (20 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (94 mg, 62.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.22 - 8.12 (m, 1H), 7.80 - 7.65 (m, 1H), 7.35 - 7.03 (m, 3H), 6.71 - 6.60 (m, 1H), 4.86 - 4.77 (m, 1H), 4.76 - 4.68 (m, 1H), 4.37 - 4.16 (m, 4H), 4.15 - 4.00 (m, 2H), 3.68 - 3.60 (m, 1H), 2.97 - 2.92 (m, 2H), 2.89 - 2.73 (m, 3H), 2.71 - 2.64 (m, 2H), 2.31 - 2.19 (m, 2H), 2.10 - 1.82 (m, 4H), 1.46 - 1.17 (m, 6H), 1.10 - 0.93 (m, 3H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.44

min, m/z = 603.3 $[M+H]^+$; HPLC (Method G): Rt = 4.20 min, 99.79%; SFC (Method AK): Rt = 1.36 min, 100%.

Example 435. 5-Fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 435)

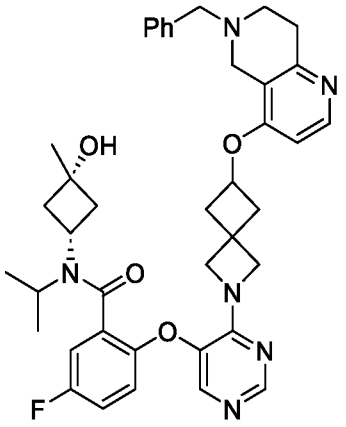


Step 1. (1s,3s)-3-(Isopropylamino)-1-methylcyclobutan-1-ol hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 434, step 1, starting with 1 equivalent of (1*s*,3*s*)-3-amino-1-methylcyclobutan-1-ol hydrochloride, to obtain crude (1*s*,3*s*)-3-(isopropylamino)-1-methylcyclobutan-1-ol hydrochloride as a gummy solid. This material was used without further purification. Yield: Quantitative; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (br s, 2H), 3.35 (spt, J = 7.1 Hz, 1H), 3.15 - 3.09 (m, 1H), 2.41 - 2.14 (m, 4H), 1.23 (br s, 3H), 1.21 (d, J = 6.5 Hz, 6H), one proton merged with solvent peaks.

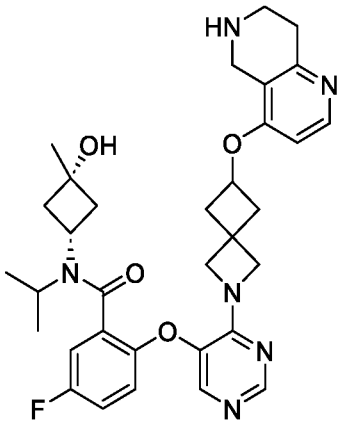
Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 434, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl, except that 3 equivalents of (1*s*,3*s*)-3-(isopropylamino)-1-methylcyclobutan-1-ol hydrochloride. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropylbenzamide (450 mg, 73.3% yield) as a solid.

Yield: 73.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.80 - 7.62 (m, 1H), 7.40 - 7.21 (m, 7H), 7.17 - 7.09 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 5.09 - 4.93 (m, 1H), 4.72 (quin, J = 6.6 Hz, 1H), 4.40 - 4.03 (m, 4H), 3.92 - 3.80 (m, 1H), 3.68 (s, 2H), 3.63 - 3.50 (m, 1H), 3.47 (s, 2H), 2.85 - 2.73 (m, 4H), 2.72 - 2.63 (m, 2H), 2.29 - 1.98 (m, 5H), 1.90 - 1.77 (m, 1H), 1.09 (m, 6H), 1.03 (m, 3H); LCMS (Method G): Rt = 2.01 min, m/z = 693.4 $[M+H]^+$, 99.42%.

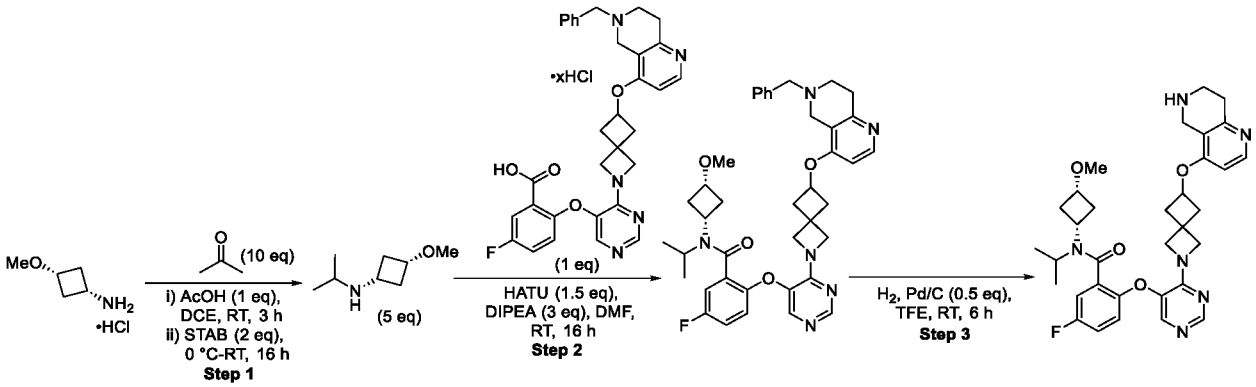
Step 3. 5-Fluoro-N-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 434, step 3, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropylbenzamide (250 mg, 0.361 mmol), except that 0.5 equivalent of Pd-C was used. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 60.4%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.23 (m, 1H), 8.22 - 8.12 (m, 1H), 7.82 - 7.61 (m, 1H), 7.33 - 6.95 (m, 3H), 6.74 - 6.60 (m, 1H), 5.22 - 5.01 (m, 1H), 4.73 (quin, *J* = 6.4 Hz, 1H), 4.42 - 4.08 (m, 4H), 3.87 - 3.68 (m, 2H), 3.65 - 3.51 (m, 2H), 2.95 (br t, *J* = 5.8 Hz, 2H), 2.89 - 2.74 (m, 4H), 2.68 (br t, *J* = 5.5 Hz, 2H), 2.31 - 2.18 (m, 2H), 2.16 - 1.97 (m, 3H), 1.51 - 1.17 (m, 6H), 1.03 (br s, 3H); LCMS (Method G): Rt = 1.48 min, m/z = 603.3 $[M+H]^+$; HPLC (Method G): Rt = 4.37 min, 99.48%; SFC (Method AAAA): Rt = 2.41 min, 100%.

Example 436. 5-Fluoro-*N*-isopropyl-*N*-((1*s*,3*s*)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 436)



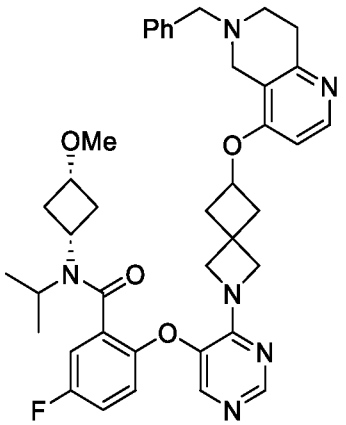
Step 1. (1s,3s)-N-Isopropyl-3-methoxycyclobutan-1-amine



In a 100 mL two neck round bottom flask under a nitrogen atmosphere, (1*s*,3*s*)-3-methoxycyclobutan-1-amine hydrochloride (1 g, 7.27 mmol) was added in DCE (10 mL). To this solution, acetone (5.34 mL, 72.7 mmol) and AcOH (0.416 mL, 7.27 mmol) were added, and the reaction was stirred at RT for 2 h. The reaction was cooled to 0 °C, sodium

triacetoxyborohydride (3.08 g, 14.53 mmol) was added, and the reaction was stirred at RT for 16 h. The reaction was quenched with $NaHCO_3$ (50 mL) and the mixture was extracted with DCM (3 x 50 mL). The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude (1*s*,3*s*)-*N*-isopropyl-3-methoxycyclobutan-1-amine (1.0 g, 96% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 - 3.44 (m, 1H), 3.10 (m, 3H), 2.80 - 2.73 (m, 1H), 2.72 - 2.65 (m, 1H), 1.90 - 1.72 (m, 2H), 1.56 - 1.40 (m, 2H), 0.92 (d, J = 6.2 Hz, 6H). One proton merged with solvent peaks. This material was used without further purification.

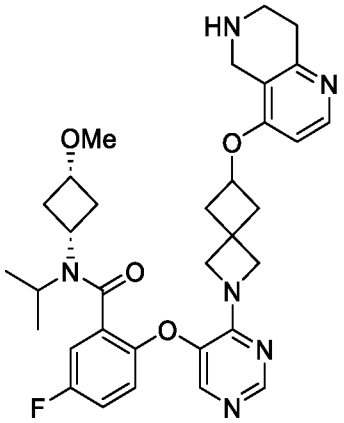
Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-((1s,3s)-3-methoxycyclobutyl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 434, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl and 5 equivalents of (1*s*,3*s*)-*N*-isopropyl-3-methoxycyclobutan-1-amine, except that 3 equivalents of DIPEA was used. After completion, the reaction was diluted with water and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude compound. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-N-((1s,3s)-3-methoxycyclobutyl)benzamide as a solid.

Yield: 48%; LCMS (Method G): Rt = 2.08 min, m/z = 693.3 $[M+H]^+$; 97.59%.

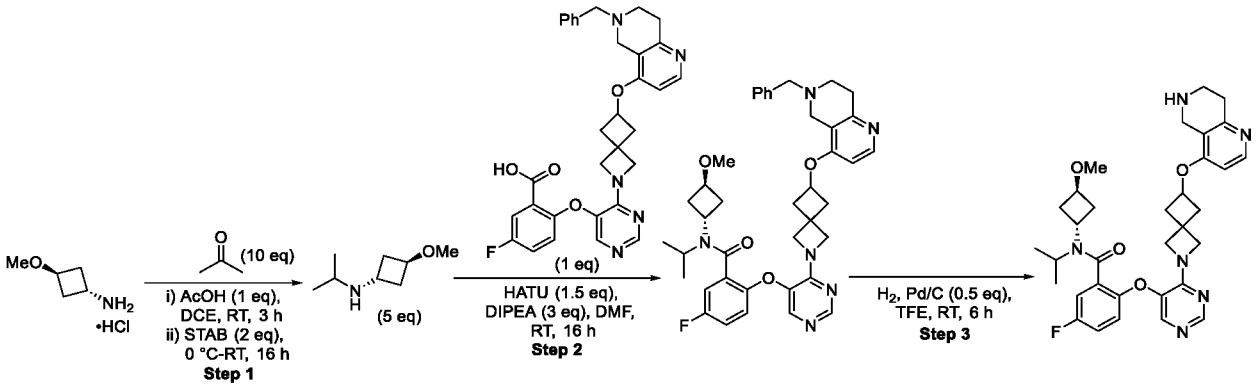
Step 3. 5-Fluoro-N-isopropyl-N-((1s,3s)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



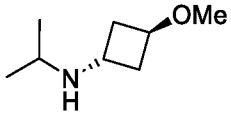
This compound was synthesized following the procedure described for the synthesis of Example 434, step 3, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-((1*s*,3*s*)-3-methoxycyclobutyl)benzamide, except that 0.5 equivalent of Pd-C was used. After completion, the reaction was filtered through a Celite® pad and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude was purified by Prep HPLC (Method C) to obtain *N*-isopropyl-*N*-((1*s*,3*s*)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 52.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.78 - 7.75 (m, 1H), 7.30 - 7.21 (m, 1H), 7.18 - 7.02 (m, 2H), 6.64 (d, J = 5.8 Hz, 1H), 4.77 - 4.68 (m, 1H), 4.32 - 4.07 (m, 4H), 3.76 - 3. 69 (brs, 3H), 3.62 - 3.39 (m, 2H), 3.16 - 3.04 (m, 3H), 2.94 (t, J = 5.8 Hz, 2H), 2.82 - 2.73 (m, 3H), 2.67 (br t, J = 5.5 Hz, 2H), 2.43 - 2.30 (m, 1H), 2.28 - 2.19 (m, 3H), 1.97 - 1.83 (m, 1H), 1.48 - 0.95 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.60 min, m/z = 603.3 $[M+H]^+$; HPLC (Method G): Rt = 4.66 min, 99.70%; SFC (Method B) = 1.50 min; 97.99%.

Example 437. 5-Fluoro-*N*-isopropyl-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 437)



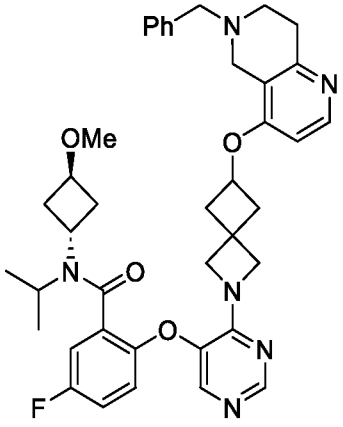
Step 1. (1r,3r)-N-Isopropyl-3-methoxycyclobutan-1-amine



This compound was synthesized following the procedure described for the synthesis of Example 436, step 1, starting with 1 equivalent of (1*r*,3*r*)-3-methoxycyclobutan-1-amine hydrochloride. After completion, the reaction was quenched with $NaHCO_3$ and extracted with DCM. The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude (1*r*,3*r*)-*N*-isopropyl-3-methoxycyclobutan-1-amine as a semi-solid. This material was used without further purification.

Yield: 96%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.94 - 3.86 (m, 1H), 3.40 - 3.32 (m, 1H), 3.11 (s, 3H), 2.73 - 2.63 (m, 1H), 2.11 - 2.01 (m, 2H), 1.93 - 1.87 (m, 2H), 0.94 (d, J = 6.3 Hz, 6H), one proton merged with solvent peaks.

Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-((1r,3r)-3-methoxycyclobutyl)benzamide

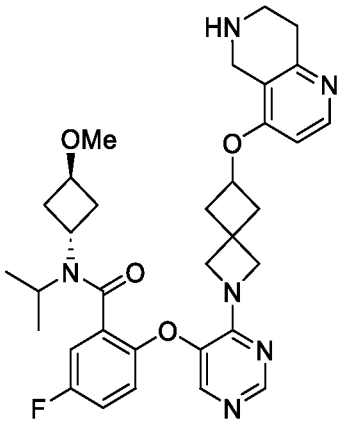


This compound was synthesized following the procedure described for the synthesis of Example 434, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-

naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl and 5 equivalents of (1*r*,3*r*)-*N*-isopropyl-3-methoxycyclobutan-1-amine, except that 3 equivalents of DIPEA was used. After completion, the reaction was diluted with water and the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-((*1r,3r*)-3-methoxycyclobutyl)benzamide as a solid.

Yield: 39.4%; LCMS (Method G): Rt = 2.10 min, m/z = 693.3 $[M+H]^+$, 96.13%.

Step 3. 5-Fluoro-N-isopropyl-N-((1r,3r)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

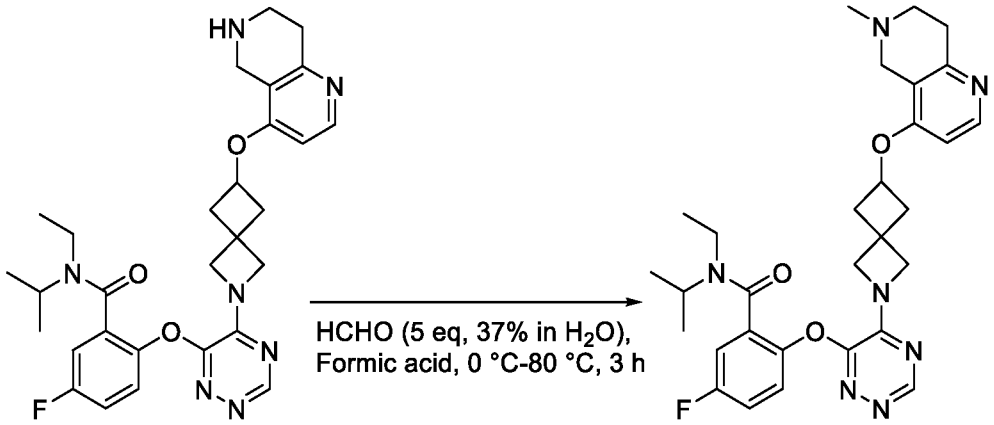


This compound was synthesized following the procedure described for the synthesis of Example 434, step 3, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)benzamide, except that 0.5 equivalent of Pd-C was used. After completion, the reaction was filtered through a Celite® pad and the pad was washed with TFE. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-isopropyl-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 18.16%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.24 (m, 1H), 8.21 - 8.13 (m, 1H), 7.78 - 7.62 (m, 1H), 7.34 - 7.22 (m, 2H), 7.19 - 7.02 (m, 2H), 6.69 - 6.61 (m, 1H), 4.79 - 4.67

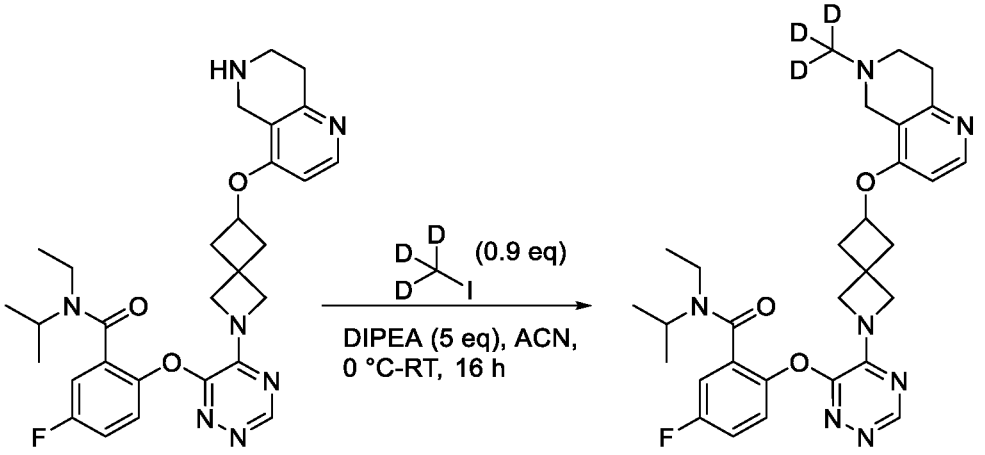
(m, 1H), 4.34 - 4.03 (m, 6H), 3.78 - 3.72 (m, 1H), 3.69 (brs, 2H), 3.16 - 3.00 (m, 3H), 2.94 (bt, *J* = 5.5 Hz, 2H), 2.84 - 2.73 (m, 3H), 2.70 - 2.64 (m, 2H), 2.26-2.21 (m, 3H), 2.19 - 1.84 (m, 1H), 1.47 - 0.91 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.58 min, m/z = 603.3 $[M+H]^+$; HPLC (Method G): Rt = 4.63 min, 98.52%; SFC (Method B) = 1.48 min; 100%.

Example 438. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 438)



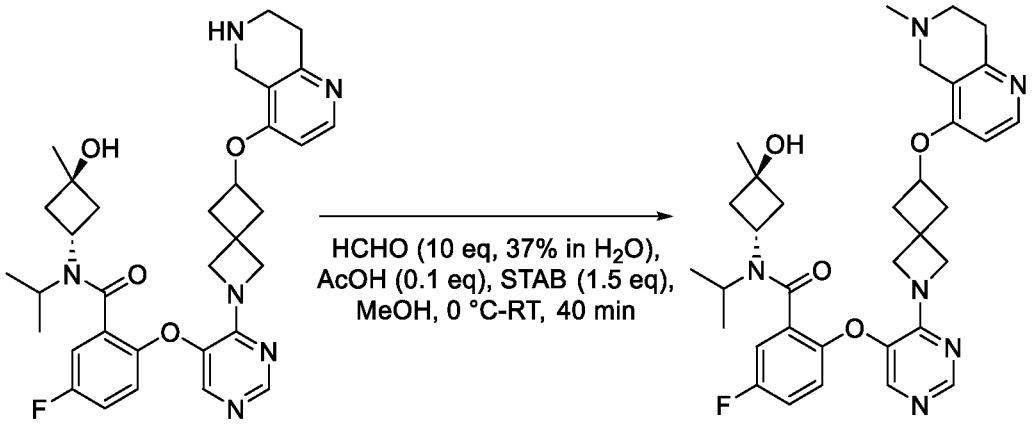
In a 50 mL two neck round bottom flask, *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (0.3 g, 0.548 mmol), formic Acid (5 mL) was added at 0 °C. To this solution, formaldehyde (0.204 mL, 2.74 mmol, 37% in H_2O) was added at 0 °C. The reaction was stirred at 80 °C for 3 h. The reaction progress was monitored by LCMS. After completion, the reaction was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method H). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (14.19 mg, 4.58% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.47 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.32 (m, 2H), 6.69 (d, *J* = 5.6 Hz, 1H), 4.79 (quin, *J* = 6.6 Hz, 1H), 4.67 - 4.48 (m, 2H), 4.32 - 4.10 (m, 2H), 3.69 - 3.55 (m, 1H), 3.38 (br s, 2H), 3.17 - 3.01 (m, 1H), 2.88 - 2.78 (m, 4H), 2.68 - 2.61 (m, 2H), 2.41 - 2.35 (m, 5H), 1.21 - 0.66 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.67 min, m/z = 562.4 $[M+H]^+$; HPLC (Method G): Rt = 4.83 min, 99.50%.

Example 439. *N*-Ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(methyl-d3)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (Compound No. 439)



To a stirred solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (0.15 g, 0.274 mmol) and DIPEA (0.177 g, 1.370 mmol) in acetonitrile (9 mL), iodomethane-d_3 (0.036 g, 0.247 mmol) was added at 0 °C. The reaction was stirred at RT for 16 h. The reaction progress was monitored by LCMS. The reaction was quenched with aq. sodium bicarbonate solution (5 mL) and the mixture was extracted with 10% MeOH in DCM (2 x 20 mL). The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method AS). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-((6-(methyl-d3)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide (18 mg, 11.47% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.40 - 7.33 (m, 2H), 6.69 (d, J = 5.6 Hz, 1H), 4.79 (quin, J = 6.6 Hz, 1H), 4.70 - 4.45 (m, 2H), 4.36 - 4.09 (m, 2H), 3.71 - 3.55 (m, 1H), 3.37 (s, 2H), 3.16 - 3.00 (m, 1H), 2.87 - 2.77 (m, 4H), 2.63 (br t, J = 5.5 Hz, 2H), 2.38 - 2.28 (m, 2H), 1.18 - 0.65 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.64 min, m/z = 565.2 $[M+H]^+$; HPLC (Method G): Rt = 4.39 min, 98.58%.

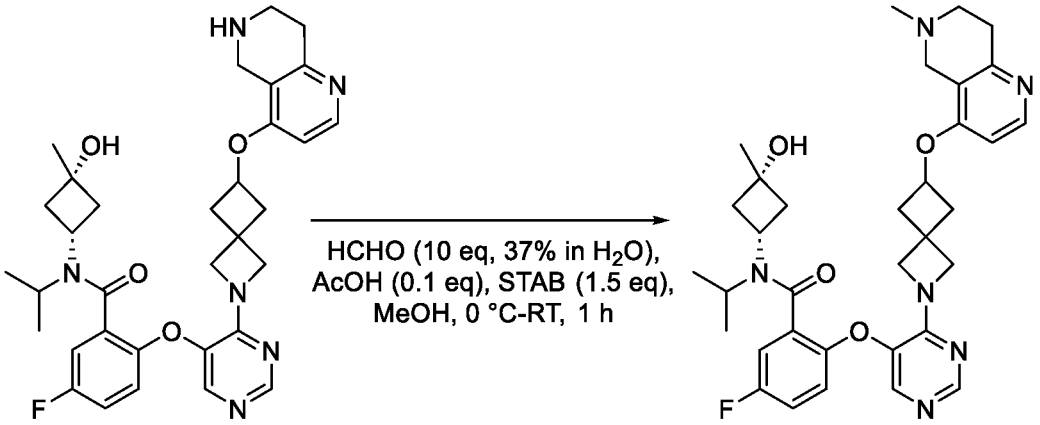
Example 440. 5-Fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 440)



This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with 1 equivalent of 5-fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and 10 equivalents of HCHO (37% in H_2O), except that 0.1 equivalent of AcOH and 1.5 equivalents of SATB were used, and MeOH was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-((1*r*,3*r*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 54.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.79 - 7.67 (m, 1H), 7.34 - 7.01 (m, 3H), 6.73 - 6.59 (m, 1H), 4.85 - 4.68 (m, 2H), 4.37 - 4.17 (m, 3H), 4.15 - 3.98 (m, 2H), 3.67 (spt, J = 6.5 Hz, 1H), 3.37 (s, 2H), 2.86 - 2.74 (m, 4H), 2.66 - 2.60 (m, 2H), 2.37 (s, 3H), 2.30 - 2.21 (m, 2H), 2.10 - 1.84 (m, 3H), 1.48 - 1.16 (m, 6H), 1.13 - 0.94 (m, 3H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.67 min, m/z = 617.4 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 99.07%; SFC (Method AB): Rt = 1.05 min, 100%.

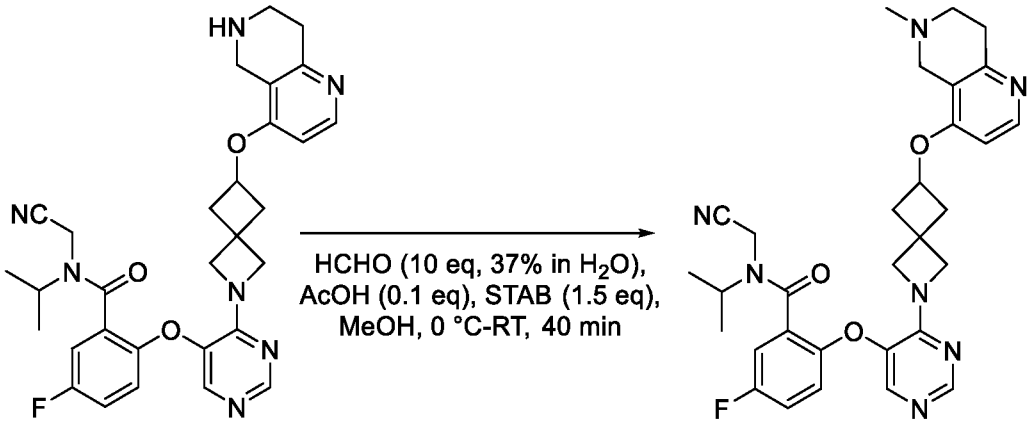
Example 441. 5-Fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 441)



This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with 1 equivalent of 5-fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and 10 equivalents of HCHO (37% in H_2O), except that 0.1 equivalent of AcOH and 1.5 equivalents of SATB were used, and MeOH was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 39.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.82 - 7.63 (m, 1H), 7.33 - 7.00 (m, 3H), 6.66 (d, J = 5.6 Hz, 1H), 5.09 - 4.96 (m, 1H), 4.74 (quin, J = 6.6 Hz, 1H), 4.34 - 4.10 (m, 4H), 3.93 - 3.67 (m, 1H), 3.65 - 3.47 (m, 1H), 3.37 (br s, 2H), 2.85 - 2.73 (m, 4H), 2.65 - 2.60 (m, 2H), 2.37 (s, 3H), 2.30 - 2.20 (m, 3H), 2.16 - 1.97 (m, 3H), 1.49 - 1.21 (m, 6H), 1.03 (s, 3H); LCMS (Method G): Rt = 1.66 min, m/z = 617.2 $[M+H]^+$; HPLC (Method G): Rt = 4.85 min, 99.64%; SFC (Method AAAB): Rt = 1.13 min, 100%.

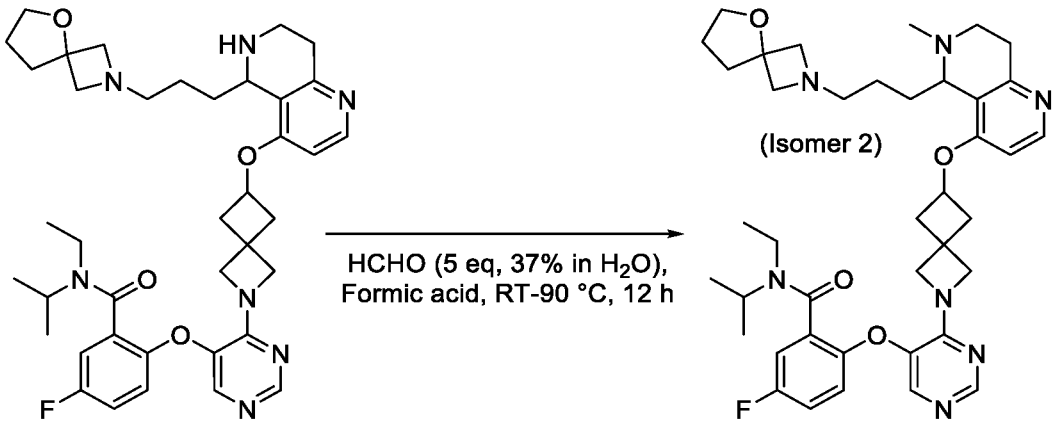
Example 442. *N*-(Cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 442)



This reaction was performed following the same procedure in two batches (50 mg and 200 mg).

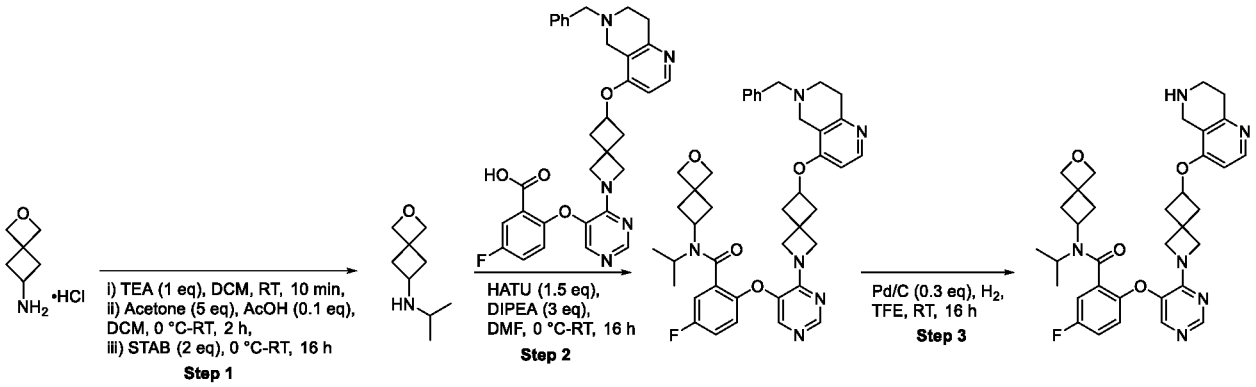
This compound was synthesized following the procedure described for the synthesis of Example 26, step 3, starting with 1 equivalent of *N*-(cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and 10 equivalents of HCHO (37% in H_2O), except that 0.1 equivalent of AcOH and 1.5 equivalents of STAB were used, and MeOH was used as a solvent. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-(cyanomethyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Combined yield: 54.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.85 (s, 1H), 7.38 (dd, J = 3.0, 8.1 Hz, 1H), 7.31 (dt, J = 3.1, 8.7 Hz, 1H), 7.05 (dd, J = 4.3, 9.1 Hz, 1H), 6.65 (d, J = 5.8 Hz, 1H), 4.72 (quin, J = 6.7 Hz, 1H), 4.46 (br d, J = 1.3 Hz, 2H), 4.32 - 4.05 (m, 4H), 3.89 (spt, J = 6.6 Hz, 1H), 3.36 (s, 2H), 2.85 - 2.72 (m, 4H), 2.63 (br t, J = 5.8 Hz, 2H), 2.36 (s, 3H), 2.29 - 2.20 (m, 2H), 1.21 - 1.06 (m, 6H); LCMS (Method G): Rt = 1.63 min, m/z = 572.3 $[M+H]^+$; HPLC (Method G): Rt = 4.80 min, 99.73%.

Example 443. (*E2*)-2-((4-(6-((5-(3-(5-Oxa-2-azaspiro[3.4]octan-2-yl)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 443)

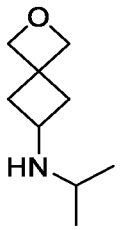


To a stirred solution of (*E2*)-2-((4-(6-((5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (40 mg, 0.057 mmol) in formic acid (2.0 mL), formaldehyde (0.021 mL, 0.286 mmol, 37% in H_2O) was added at RT. The reaction was stirred at 90 °C for 12 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*E2*)-2-((4-(6-((5-(3-(5-oxa-2-azaspiro[3.4]octan-2-yl)propyl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (20 mg, 48.4% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.25 (m, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.78 - 7.60 (m, 1H), 7.36 - 7.20 (m, 2H), 7.15 - 7.00 (m, 1H), 6.71 - 6.60 (m, 1H), 4.80 - 4.69 (m, 1H), 4.33 - 4.09 (m, 4H), 3.75 (td, *J* = 6.6, 13.1 Hz, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.53 (br t, *J* = 5.8 Hz, 1H), 3.44 - 3.37 (m, 1H), 3.25 - 3.06 (m, 5H), 2.90 - 2.66 (m, 6H), 2.39 - 2.33 (m, 2H), 2.30 (s, 3H), 2.27 - 2.16 (m, 2H), 1.98 - 1.91 (m, 2H), 1.76 (quin, *J* = 6.9 Hz, 2H), 1.59 - 1.46 (m, 2H), 1.45 - 1.30 (m, 2H), 1.23 - 0.98 (m, 9H); LCMS (Method J): Rt = 3.11 min, m/z = 714.3 $[M+H]^+$; HPLC (Method G): Rt = 5.08 min, 99.40%; SFC (Method AL): Rt = 6.40 min, 98.74%.

Example 444. 5-Fluoro-*N*-isopropyl-*N*-(2-oxaspiro[3.3]heptan-6-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 444)



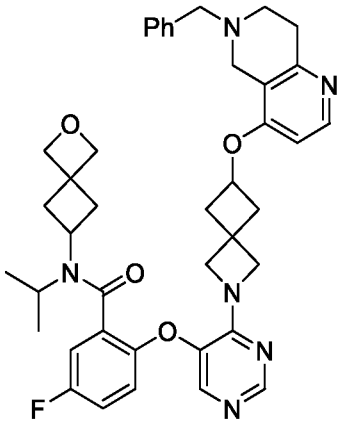
Step 1. N-Isopropyl-2-oxaspiro[3.3]heptan-6-amine



This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of 2-oxaspiro[3.3]heptan-6-amine hydrochloride and 5 equivalents of acetone, except that 1 equivalent of TEA, 0.1 equivalent of AcOH and 2 equivalents of STAB were used, and DCM was used as a solvent. After completion, the reaction was quenched with saturated sodium bicarbonate solution and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford crude *N*-isopropyl-2-oxaspiro[3.3]heptan-6-amine as a liquid. This material was used without further purification.

Yield: 54.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.55 (s, 2H), 4.43 (s, 2H), 3.06 - 2.97 (m, 1H), 2.65 (spt, J = 6.3 Hz, 1H), 2.44 - 2.37 (m, 2H), 1.84 - 1.75 (m, 2H), 0.90 (d, J = 6.3 Hz, 6H), one proton merged with solvent peaks; LCMS-ELSD (Method G): Rt = 1.67 min, m/z = 492.1 $[M+H]^+$, 89.78%.

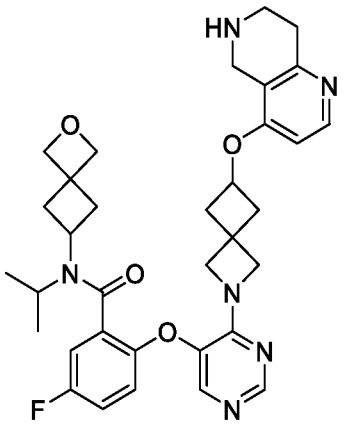
Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(2-oxaspiro[3.3]heptan-6-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl and 1 equivalent of *N*-isopropyl-2-oxaspiro[3.3]heptan-6-amine. After completion, the reaction was diluted with water and the mixture was extracted with EtOAc. The combined organic layer was washed with cold water and brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 8% MeOH in DCM) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2-oxaspiro[3.3]heptan-6-yl)benzamide as a solid.

Yield: 35.8%; LCMS (Method G): Rt = 2.0 min, m/z = 705.3 $[M+H]^+$, 59.21%.

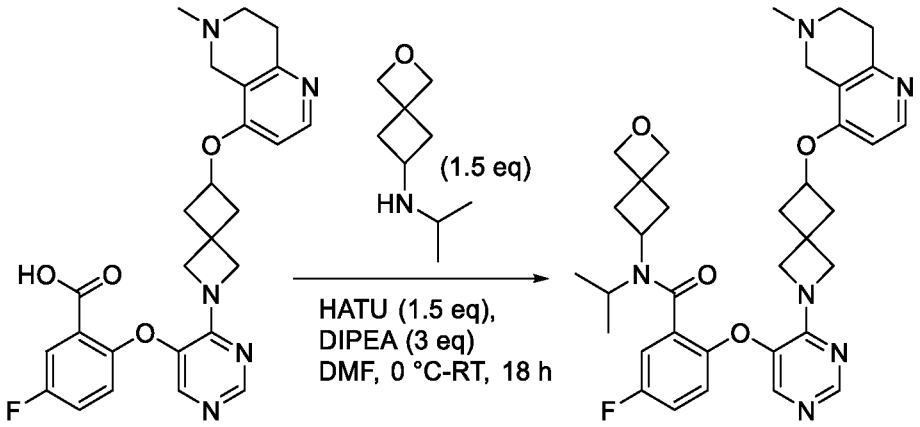
Step 3. 5-Fluoro-N-isopropyl-N-(2-oxaspiro[3.3]heptan-6-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(2-oxaspiro[3.3]heptan-6-yl)benzamide, except that 0.3 equivalent of Pd/C was

used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (60 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-*N*-(2-oxaspiro[3.3]heptan-6-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 51.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.79 - 7.72 (m, 1H), 7.32 - 7.21 (m, 2H), 7.16 - 7.02 (m, 1H), 6.64 (d, J = 5.6 Hz, 1H), 4.73 (quin, J = 6.4 Hz, 1H), 4.62 - 4.49 (m, 3H), 4.42 (br s, 1H), 4.34 - 4.08 (m, 4H), 3.93 - 3.75 (m, 1H), 3.73 - 3.61 (m, 3H), 3.15 - 3.05 (m, 1H), 2.94 (br t, J = 5.9 Hz, 2H), 2.85 - 2.74 (m, 3H), 2.71 - 2.65 (m, 2H), 2.46 - 2.36 (m, 1H), 2.32 - 2.17 (m, 3H), 1.44 - 0.89 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.51 min, m/z = 615.3 $[M+H]^+$; HPLC (Method G): Rt = 4.46 min, 97.04%.

Example 445. 5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2-oxaspiro[3.3]heptan-6-yl)benzamide (Compound No. 445)



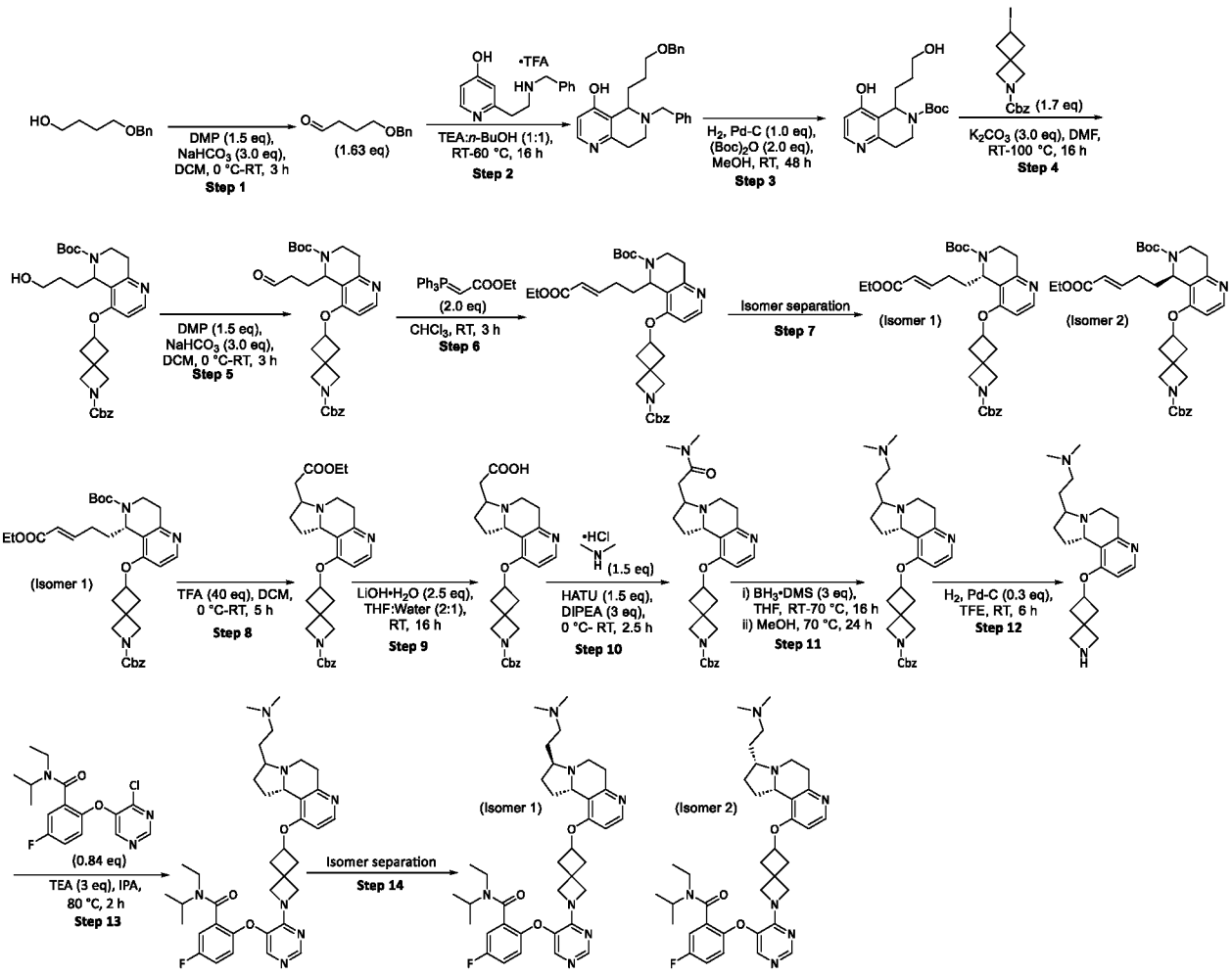
This compound was synthesized following the procedure described for the synthesis of Example 9, step 3, starting with 1 equivalent of 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic and 1.5 equivalents of *N*-isopropyl-2-oxaspiro[3.3]heptan-6-amine. After completion, the reaction was diluted with water and the mixture was extracted with EtOAc. The combined organic layer was washed with cold water and brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure.

The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method AS). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(2-oxaspiro[3.3]heptan-6-yl)benzamide as a solid.

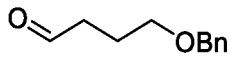
Yield: 7.78%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.78 - 7.74 (m, 1H), 7.31 - 7.21 (m, 2H), 7.16 - 7.02 (m, 1H), 6.66 (d, J = 5.6 Hz, 1H), 4.75 (quin, J = 6.5 Hz, 1H), 4.61 - 4.50 (m, 3H), 4.42 (br s, 1H), 4.33 - 4.08 (m, 4H), 3.95 - 3.75 (m, 1H), 3.72 - 3.58 (m, 1H), 3.36 (s, 2H), 3.17 - 2.87 (m, 2H), 2.84 - 2.75 (m, 4H), 2.63 (br t, J = 5.7 Hz, 2H), 2.47 - 2.39 (m, 1H), 2.36 (s, 3H), 2.31 - 2.21 (m, 3H), 1.45 - 0.91 (m, 6H); LCMS (Method G): Rt = 2.02 min, m/z = 629.3 $[M+H]^+$; HPLC (Method A): Rt = 4.97 min, 99.53%.

Example 446. 2-((4-(6-(((8*S*,10a*S*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 446)

Example 447. 2-((4-(6-(((8*R*,10a*S*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 447)

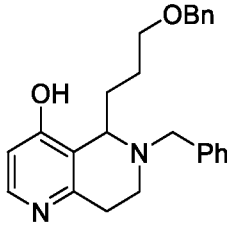


Step 1. 4-(Benzyloxy)butanal



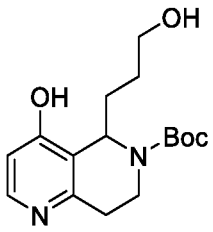
To a stirred solution of 4-(benzyloxy)butan-1-ol (10.0 g, 55.5 mmol) in DCM (150 mL), sodium bicarbonate (13.98 g, 166 mmol) and DMP (35.3 g, 83 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h. The progress of the reaction was monitored by TLC (20% EtOAc in hexane). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with DCM (3 x 100 mL). The filtrate was washed with sodium bicarbonate solution (3 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was dissolved in hexane (150 mL) and stirred at RT for 15 minutes. The mixture was filtered through a Celite® pad and the pad was washed with hexane (3 x 100 mL). The filtrate was concentrated under reduced pressure to obtain crude 4-(benzyloxy)butanal (9.44 g, 95% yield) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (t, J = 1.6 Hz, 1H), 7.40 - 7.30 (m, 5H), 4.51 (s, 2H), 3.54 (t, J = 6.1 Hz, 2H), 2.58 (dt, J = 1.5, 7.1 Hz, 2H), 2.02 - 1.94 (m, 2H). This material was used without further purification.

Step 2. (±)-6-Benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol



To a stirred solution of 2-(2-(benzylamino)ethyl)pyridin-4-ol 2,2,2-trifluoroacetic acid (11 g, 32.1 mmol) in *n*-butanol (50 mL), triethylamine (50 mL) and 4-(benzyloxy)butanal (9.34 g, 52.4 mmol) was added at RT. The reaction was stirred at 60 °C for 16 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT, quenched with water (100 mL) and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 5-10% MeOH in DCM) to afford (±)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (8.77 g, 63.9% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.18 (s, 1H), 7.52 - 7.46 (m, 1H), 7.38 - 7.20 (m, 10H), 5.92 (J = 7.2 Hz), 4.40 (s, 2H), 3.67 (d, J = 13.4 Hz, 1H), 3.52 (d, J = 13.5 Hz, 1H), 3.48 - 3.43 (m, 1H), 3.18 - 3.00 (m, 2H), 2.81 - 2.65 (m, 2H), 2.29 - 2.19 (m, 1H), 1.82 - 1.64 (m, 2H), 1.57 - 1.47 (m, 1H), 1.46 - 1.35 (m, 1H), one proton merged with solvent peaks; LCMS (Method D): Rt = 1.82 min, m/z = 389.2 $[M+H]^+$, 91.20%.

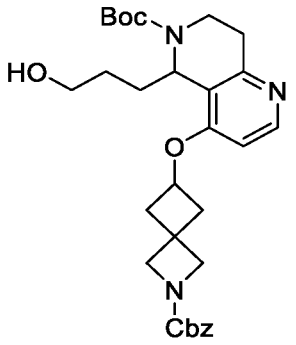
Step 3. (±)-tert-Butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 1 L three neck round bottom flask under an argon atmosphere, (±)-6-benzyl-5-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-ol (8.77 g, 22.57 mmol) was added in MeOH (150 mL). To this solution, $(Boc)_2O$ (10.37 mL, 45.1 mmol) and Pd-C (12.01 g, 22.57 mmol) were added, and the reaction was stirred at RT for 16 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by LCMS. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with

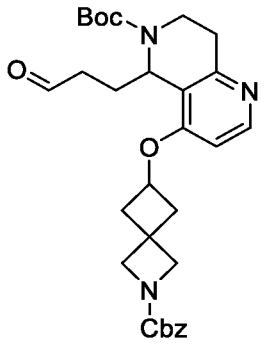
MeOH (3 x 100 mL). The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted at 10% MeOH in DCM) to obtain (±)-*tert*-butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (4.5 g, 62.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (s, 1H), 7.54 (d, J = 6.9 Hz, 1H), 6.00 (d, J = 6.9 Hz, 1H), 4.99 - 4.84 (m, 1H), 4.54 - 4.42 (m, 1H), 4.20 - 3.94 (m, 1H), 3.42 (br s, 2H), 3.21 - 3.00 (m, 1H), 2.66 - 2.57 (m, 2H), 1.92 - 1.79 (m, 1H), 1.54 - 1.43 (m, 3H), 1.41 (s, 9H); LCMS (Method G): Rt = 1.16 min, m/z = 309.1 $[M+H]^+$, 96.32%.

Step 4. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



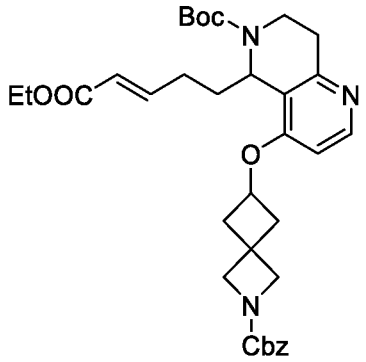
To a stirred solution of (±)-*tert*-butyl 4-hydroxy-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (7.9 g, 25.6 mmol) and benzyl 6-iodo-2-azaspiro[3.3]heptane-2-carboxylate (15.56 g, 43.6 mmol) in DMF (100 mL), K_2CO_3 (10.62 g, 77 mmol) was added at RT. The reaction was stirred at 100 °C for 12 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT and diluted with cold water (100 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 5-10% MeOH in DCM) to obtain (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (10.78 g, 69.7% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 5.5 Hz, 1H), 7.40 - 7.29 (m, 5H), 6.70 (d, J = 5.6 Hz, 1H), 5.19 - 5.05 (m, 1H), 5.03 (s, 2H), 4.81 - 4.71 (m, 1H), 4.43 - 4.33 (m, 1H), 4.18 - 4.09 (m, 1H), 4.07 - 3.92 (m, 4H), 3.53 - 3.39 (m, 2H), 3.26 - 3.14 (m, 1H), 2.82 - 2.71 (m, 4H), 2.30 - 2.17 (m, 2H), 1.83 - 1.73 (m, 1H), 1.65 - 1.45 (m, 3H), 1.41 (s, 9H); LCMS (Method B): Rt = 1.51 min, m/z = 538.2 $[M+H]^+$, 89.03%.

Step 5. (±)-tert-Butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-oxopropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-hydroxypropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (10.7 g, 19.90 mmol) in DCM (120 mL), sodium bicarbonate (5.02 g, 59.7 mmol) and DMP (12.66 g, 29.9 mmol) were added at 0 °C. The reaction was stirred at RT for 4 h. The progress of the reaction was monitored by TLC (100% EtOAc). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with DCM (3 x 100 mL). The filtrate was washed with sodium bicarbonate solution (3 x 150 mL). The combined organic layer was dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain crude (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-oxopropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (16.58 g, 76% yield). LCMS (Method G): Rt = 2.17 min, m/z = 536.3 $[M+H]^+$, 49.01%. This material was used without further purification.

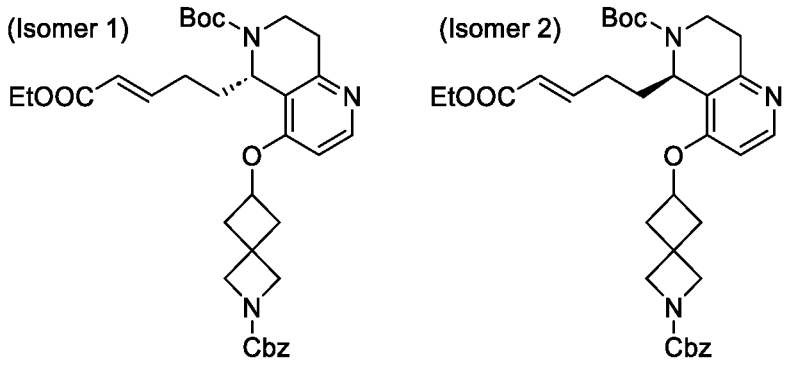
Step 6. (±)-tert-Butyl (E)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of (±)-*tert*-butyl 4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(3-oxopropyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (16.5 g, 15.09 mmol) in chloroform (150 mL), ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (10.52 g, 30.2 mmol) was added and the reaction was stirred at RT for 3 h. The progress of the reaction

was monitored by TLC (100% EtOAc). After completion, the reaction was concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using MeOH in DCM (the product was eluted at 4-5% MeOH in DCM) to obtain (±)-*tert*-butyl (*E*)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (8.76 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 - 8.22 (m, 1H), 7.40 - 7.29 (m, 5H), 7.15 - 6.96 (m, 1H), 6.71 (d, *J* = 5.7 Hz, 1H), 6.04 - 5.91 (m, 1H), 5.22 - 5.12 (m, 1H), 5.03 (s, 2H), 4.85 - 4.69 (m, 1H), 4.11 - 4.07 (q, *J* = 7.1 Hz, 2H), 4.07 - 3.89 (m, 4H), 2.83 - 2.72 (m, 4H), 2.31 - 2.17 (m, 4H), 1.89 - 1.76 (m, 2H), 1.41-1.36 (m, 9H), 1.24 (br s, 3H), two protons merged with solvent peaks; LCMS (Method G): Rt = 2.35 min, m/z = 606.5 $[M+H]^+$, 97.92%.

Step 7. tert-Butyl (S,E)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and tert-butyl (R,E)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



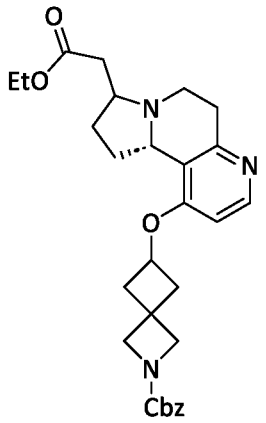
(±)-*tert*-Butyl (*E*)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (8.75 g, 14.45 mmol) was purified by chiral Prep SFC (Method AU) to afford both isomers, *tert*-butyl (*S,E*)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (3.6 g, 39.4% yield) and *tert*-butyl (*R,E*)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (3.6 g, 39.4% yield) (3.3 g, 36.2% yield) as semi-solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 - 8.22 (m, 1H), 7.40 - 7.29 (m, 5H), 7.16 - 6.95 (m, 1H), 6.71 (d, *J* = 5.7 Hz, 1H), 6.06 - 5.88 (m, 1H), 5.23 - 5.09 (m, 1H), 5.03 (s, 2H), 4.83 - 4.70 (m, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 4.06 - 3.90 (m, 4H), 2.83 - 2.71 (m, 4H), 2.31 - 2.18 (m, 4H), 1.88 - 1.77 (m, 2H), 1.41-1.36 (m, 9H), 1.23 - 1.15 (m, 3H), two protons

merged with solvent peaks; LCMS (Method B): Rt = 1.91 min, m/z = 606.8 $[M+H]^+$, 95.66%; Chiral SFC (Method AAAC): Rt = 2.25 min, 100%.

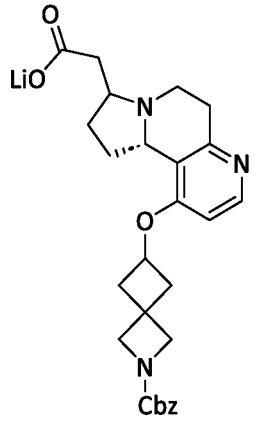
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 - 8.22 (m, 1H), 7.40 - 7.29 (m, 5H), 7.15 - 6.95 (m, 1H), 6.71 (d, J = 5.6 Hz, 1H), 6.04 - 5.90 (m, 1H), 5.22 - 5.11 (m, 1H), 5.03 (s, 2H), 4.83 - 4.69 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.06 - 3.90 (m, 4H), 2.83 - 2.71 (m, 4H), 2.32 - 2.19 (m, 4H), 1.91 - 1.74 (m, 2H), 1.41-136 (m, 9H), 1.23 - 1.16 (m, 3H), two protons merged with solvent peaks; LCMS (Method B): Rt = 1.91 min, m/z = 606.3 $[M+H]^+$; 96.05%; Chiral SFC (Method AAAC): Rt = 2.97 min, 99.72%.

Step 8. Benzyl 6-(((10aS)-8-(2-ethoxy-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



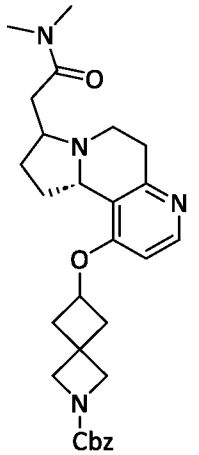
To a stirred solution of *tert*-butyl (*S,E*)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (3.6 g, 5.94 mmol) in DCM (40 mL), TFA (18.32 mL, 238 mmol) was added at 0 °C. The reaction was stirred at RT for 5 h. The progress of the reaction was monitored by TLC (5% MeOH in DCM). After completion, the reaction was cooled to 0 °C, quenched with 10% $NaHCO_3$ solution (100 mL), and the mixture was extracted with DCM (3 x 80 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude benzyl 6-(((10a*S*)-8-(2-ethoxy-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (3.00 g, 63.7% yield) as a semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (d, J = 5.5 Hz, 1H), 7.40 - 7.29 (m, 5H), 6.67 (d, J = 5.6 Hz, 1H), 5.03 (s, 2H), 4.76 - 4.66 (m, 1H), 4.17 (t, J = 7.2 Hz, 1H), 4.11 - 3.91 (m, 6H), 3.05 - 2.90 (m, 1H), 2.85 - 2.70 (m, 4H), 2.62 - 2.54 (m, 2H), 2.42 - 2.29 (m, 2H), 2.29 - 2.17 (m, 2H), 2.05 - 1.92 (m, 1H), 1.58 - 1.39 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H), one proton merged with solvent peaks; LCMS (Method G): Rt = 2.17 min, m/z = 506.3 $[M+H]^+$, 96.98%.

Step 9. Lithium 2-((10aS)-1-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-8-yl)acetate



To a stirred solution of benzyl 6-(((10a*S*)-8-(2-ethoxy-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (2.15 g, 4.25 mmol) in THF (20 mL), LiOH.H_2O (0.446 g, 10.63 mmol, 10 mL H_2O) was added at 0 °C. The reaction was stirred at RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and the residue was co-distilled with toluene (3 x 20 mL). The resulting residue was dried under reduced pressure to obtain crude lithium 2-((10a*S*)-1-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)acetate (2.15 g, quantitative yield) as a solid. LCMS (Method G): Rt = 1.46 min, m/z = 478.2 $[M+H]^+$, 93.47%. This material was used without further purification.

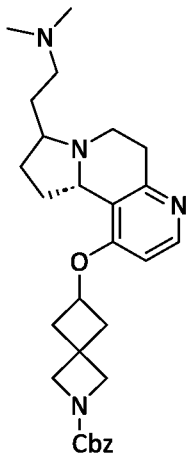
Step 10. Benzyl 6-(((10aS)-8-(2-(dimethylamino)-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of lithium 2-((10a*S*)-1-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)acetate (2.15 g, 4.45

mmol) and dimethylamine hydrochloride (0.544 g, 6.67 mmol) in DMF (10 mL), DIPEA (2.324 mL, 13.34 mmol) and HATU (2.54 g, 6.67 mmol) were added at 0 °C. The reaction was stirred RT for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was diluted with cold water (50 mL) and the mixture was extracted with EtOAc (3 x 75 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain benzyl 6-(((10a*S*)-8-(2-(dimethylamino)-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1.52 g, 67.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (d, J = 5.6 Hz, 1H), 7.40 - 7.29 (m, 5H), 6.67 (d, J = 5.6 Hz, 1H), 5.03 (s, 2H), 4.76 - 4.66 (m, 1H), 4.18 (t, J = 7.4 Hz, 1H), 4.06 - 3.90 (m, 4H), 3.27 - 3.19 (m, 1H), 3.05 - 3.00 (m, 1H), 3.00 - 2.98 (m, 3H), 2.84 - 2.81 (m, 3H), 2.80 - 2.72 (m, 4H), 2.69 - 2.55 (m, 2H), 2.45 - 2.32 (m, 1H), 2.32 - 2.17 (m, 3H), 2.10 - 1.93 (m, 1H), 1.55 - 1.37 (m, 2H); LCMS (Method G): Rt = 1.83 min, m/z = 505.3 $[M+H]^+$, 99.83%.

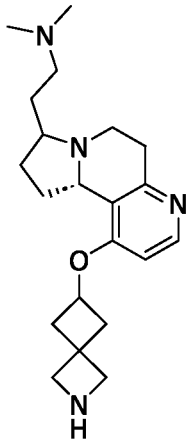
Step 11. Benzyl 6-(((10aS)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



To a stirred solution of benzyl 6-(((10a*S*)-8-(2-(dimethylamino)-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (1 g, 1.982 mmol) in THF (15 mL), borane dimethylsulfide complex (5.94 mL, 5.94 mmol, 1M in THF) was added at 0 °C under a nitrogen atmosphere. The reaction was slowly warmed to RT and stirred at 70 °C for 16 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM) and LCMS. After completion, the reaction was cooled to 0 °C, quenched with methanol (15 mL) and stirred at 70 °C for 24 h. The reaction was cooled to RT and

concentrated under reduced pressure. The residue was diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: MeOH) to obtain benzyl 6-(((10a*S*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (390 mg, 38.5% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (d, J = 5.5 Hz, 1H), 7.40 - 7.29 (m, 5H), 6.68 - 6.62 (m, 1H), 5.03 (s, 2H), 4.76 - 4.65 (m, 1H), 4.16 (t, J = 7.4 Hz, 1H), 4.07 - 3.85 (m, 4H), 3.27 - 3.20 (m, 1H), 3.06 - 2.97 (m, 1H), 2.95 - 2.85 (m, 1H), 2.82 - 2.70 (m, 4H), 2.66 - 2.55 (m, 2H), 2.46 - 2.31 (m, 2H), 2.19 (s, 6H), 1.96 - 1.84 (m, 2H), 1.74 - 1.63 (m, 1H), 1.51 - 1.29 (m, 3H); LCMS (Method G): Rt = 1.78 min, m/z = 491.2 $[M+H]^+$, 95.95%.

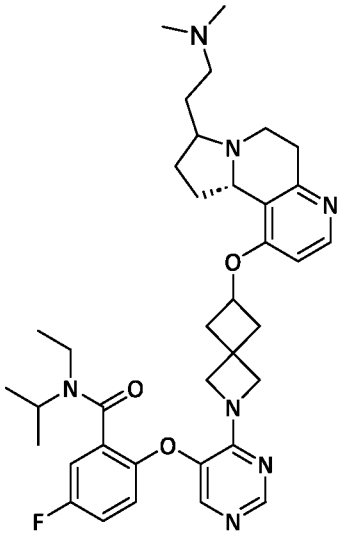
Step 12. 2-((10aS)-1-((2-Azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-8-yl)-N,N-dimethylethan-1-amine



In a 100 mL round bottom flask under an argon atmosphere, benzyl 6-(((10a*S*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate was dissolved in 2,2,2-trifluoroethanol (15 mL). To this solution, Pd-C (0.254 g, 0.238 mmol) was added, and the reaction was stirred at RT for 6 h under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by TLC (10% MeOH in DCM) and LCMS. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with TFE (5 x 30 mL). The filtrate was concentrated under reduced pressure to obtain crude 2-((10a*S*)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)-*N*,*N*-dimethylethan-1-

amine (0.270 g, 85% yield) as a semi-solid. LCMS (Method B): Rt = 0.15 min, m/z = 357.4 $[M+H]^+$, 89.11%. This material was used without further purification.

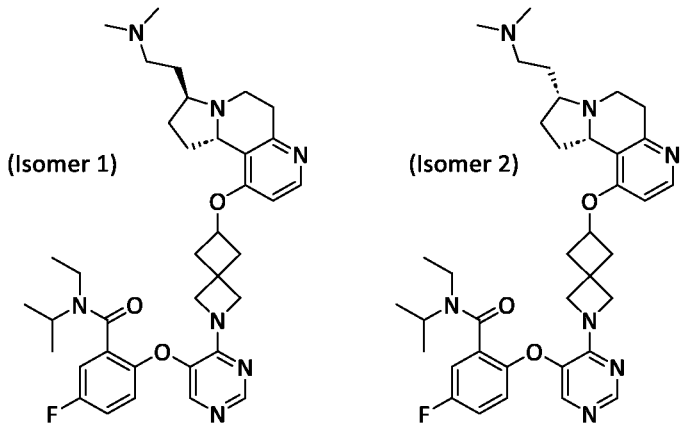
Step 13. 2-((4-(6-(((10aS)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



Step 13 was performed following the same procedure in two batches (23 mg and 230 mg). To a solution of 2-((10a*S*)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)-*N*,*N*-dimethylethan-1-amine (0.230 g, 0.645 mmol) in IPA (6 mL), TEA (0.270 mL, 1.935 mmol) was added at RT. To this reaction mixture, 2-((4-chloropyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.183 g, 0.542 mmol) was added and the reaction was stirred at 80 °C for 2 h. The progress of the reaction was monitored by LCMS. After completion, the reaction was cooled to RT. The reaction mixtures from both batches were combined and diluted with water (50 mL), and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain crude 2-((4-(6-(((10a*S*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.45 g, 96.52% combined yield) as a solid. LCMS (Method G): Rt = 1.58 min, m/z = 658.2 $[M+H]^+$; HPLC (Method G): Rt = 4.84 min, 80.30%; Chiral SFC (Method AAAD): Peak 1: Rt = 3.34 min, 74.03%; Peak 2: Rt = 5.10 min, 22.01%.

Step 14. 2-((4-(6-(((8S,10aS)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((4-(6-(((8R,10aS)-8-(2-

(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



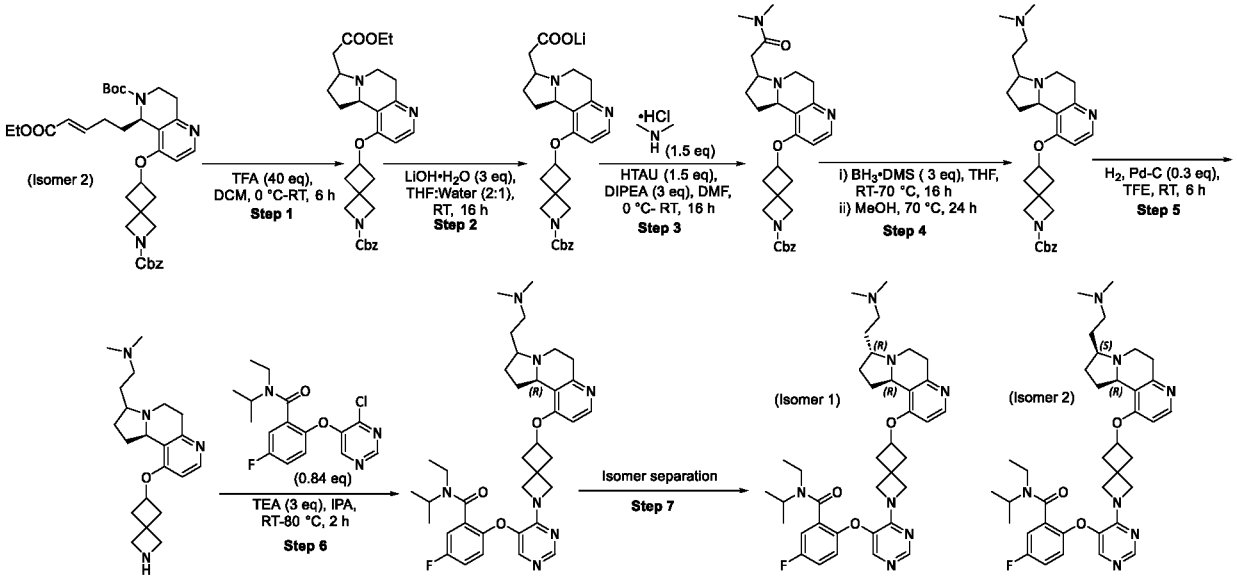
2-((4-(6-(((10a*S*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (0.42 g, 0.638 mmol) was purified by chiral Prep SFC (Method AV) to obtain both diastereomers, 2-((4-(6-(((8*S*,10a*S*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (97 mg, 22.29% yield) and 2-((4-(6-(((8*R*,10a*S*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (10 mg, 2.35% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.26 (m, 1H), 8.17 - 8.13 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.70 - 6.65 (m, 1H), 4.78 - 4.70 (m, 1H), 4.48 - 4.06 (m, 4H), 3.82 - 3.69 (m, 1H), 3.45 - 3.35 (m, 1H), 3.28 - 3.10 (m, 2H), 3.08 - 2.95 (m, 1H), 2.94 - 2.85 (m, 1H), 2.84 - 2.72 (m, 4H), 2.64 - 2.56 (m, 1H), 2.42 - 2.35 (m, 1H), 2.32 - 2.17 (m, 4H), 2.12 (s, 6H), 1.94 - 1.84 (m, 1H), 1.74 - 1.63 (m, 1H), 1.53 - 1.41 (m, 1H), 1.40 - 1.29 (m, 2H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.78 min, m/z = 658.4 $[M+H]^+$; HPLC (Method G): Rt = 4.77 min, 96.53%; Chiral SFC (Method AAAD): Rt = 2.99 min, 98.14%.

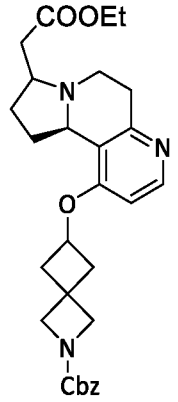
Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.26 (m, 1H), 8.19 - 8.13 (m, 1H), 7.78 - 7.65 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.67 - 6.61 (m, 1H), 4.76 - 4.69 (m, 1H), 4.46 - 4.07 (m, 4H), 3.80 - 3.70 (m, 1H), 3.27 - 3.20 (m, 2H), 3.19 - 3.11 (m, 2H), 3.09 - 2.90 (m, 2H), 2.82 - 2.72 (m, 3H), 2.46 - 2.38 (m, 2H), 2.30 - 2.18 (m, 4H), 2.14 (s, 6H), 1.95 - 1.82 (m, 2H), 1.51 - 1.30 (m, 3H), 1.22 - 0.97 (m, 9H); LCMS (Method G): Rt = 1.82 min, m/z = 658.3 $[M+H]^+$; HPLC (Method G): Rt = 4.80 min, 99.01%; Chiral SFC (Method AAAD): Rt = 4.90 min, 100%.

Example 448. 2-((4-(6-(((8*R*,10a*R*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 448)

Example 449. 2-((4-(6-(((8*S*,10a*R*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (Compound No. 449)



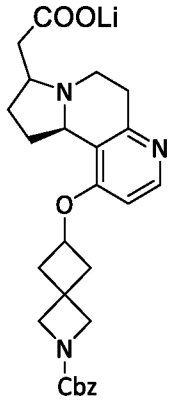
Step 1. Benzyl 6-(((10aR)-8-(2-ethoxy-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 446 and 447, Step 8, starting with 1 equivalent of *tert*-butyl (*R,E*)-4-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5-(5-ethoxy-5-oxopent-3-en-1-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate to obtain crude benzyl 6-(((*10aR*)-8-(2-ethoxy-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a semi-solid.

Yield: 98%; LCMS (Method B): Rt = 1.36 min, m/z = 506.2 $[M+H]^+$, 99.87%. This material was used without further purification.

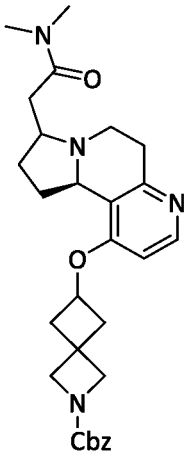
Step 2. Lithium 2-((10aR)-1-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-8-yl)acetate



This compound was synthesized following the procedure described for the synthesis of Example 446 and 447, Step 9, starting with 1 equivalent of benzyl 6-(((10a*R*)-8-(2-ethoxy-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate, except that 3 equivalents of (lithium hydroxide monohydrate was used to obtain crude lithium 2-((10a*R*)-1-((2-((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)acetate as a solid.

Yield: 84%; LCMS (Method G): Rt = 1.39 min, m/z = 478.1 $[M+H]^+$, 84.24%. This material was used without further purification.

Step 3. Benzyl 6-(((10aR)-8-(2-(dimethylamino)-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

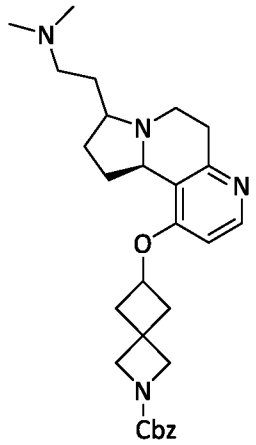


This compound was synthesized following the procedure described for the synthesis of Example 446 and 447, Step 10, starting with 1 equivalent of lithium 2-((10a*R*)-1-((2-

((benzyloxy)carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)acetate and 1.5 equivalents of dimethylamine hydrochloride. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford benzyl 6-(((10a*R*)-8-(2-(dimethylamino)-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a semi-sold.

Yield: 44.7%; LCMS (Method G): Rt = 1.62 min, m/z = 505.2 $[M+H]^+$, 99.68%.

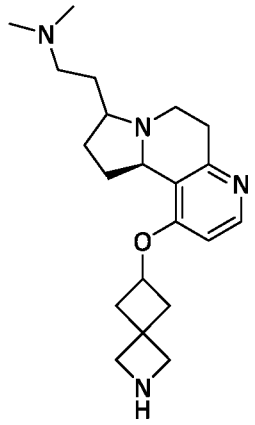
Step 4. Benzyl 6-(((10aR)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 446 and 447, Step 11, starting with 1 equivalent of of afford benzyl 6-(((10a*R*)-8-(2-(dimethylamino)-2-oxoethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g cartridge) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to afford benzyl 6-(((10a*R*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate as a semi-solid.

Yield: 52.5%; ^1H NMR (400 MHz, DMSO-d_6): 8.20 - 8.12 (m, 1H), 7.41 - 7.28 (m, 5H), 6.68 - 6.59 (m, 1H), 5.03 (s, 2H), 4.76 - 4.65 (m, 1H), 4.16 (t, J = 7.3 Hz, 1H), 4.06 - 3.84 (m, 5H), 3.26 - 3.15 (m, 1H), 3.06 - 2.95 (m, 1H), 2.95 - 2.85 (m, 1H), 2.83 - 2.70 (m, 4H), 2.64 - 2.56 (m, 2H), 2.44 - 2.32 (m, 2H), 2.32 - 2.16 (m, 5H), 1.96 - 1.86 (m, 2H), 1.74 - 1.63 (m, 1H), 1.52 - 1.42 (m, 1H), 1.41 - 1.29 (m, 2H); LCMS (Method G): Rt = 1.79 min, m/z = 491.2 $[M+H]^+$; 94.02%.

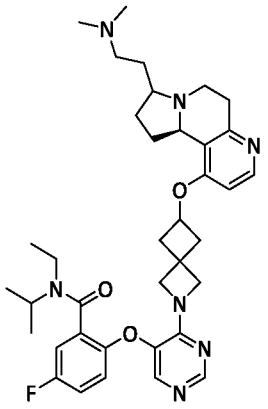
Step 5. 2-((10aR)-1-((2-Azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-8-yl)-N,N-dimethylethan-1-amine



This compound was synthesized following the procedure described for the synthesis of Example 446 and 447, Step 12, starting with 1 equivalent of benzyl 6-(((10a*R*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate to obtain crude 2-((10a*R*)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)-*N*,*N*-dimethylethan-1-amine as a semi-solid.

Yield: Quantitative; LCMS (Method B): Rt = 0.15 min, m/z = 357.3 $[M+H]^+$, 95.97%. This material was used without further purification.

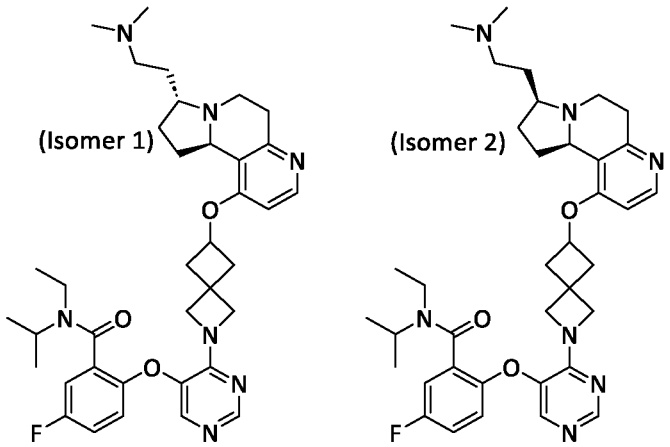
Step 6. 2-((4-(6-(((10aR)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



This compound was synthesized following the procedure described for the synthesis of Example 446 and 447, Step 13, starting with 1 equivalent of 2-((10a*R*)-1-((2-azaspiro[3.3]heptan-6-yl)oxy)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-8-yl)-*N*,*N*-dimethylethan-1-amine. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10

mM NH_4HCO_3 in water, B: MeOH) to obtain 2-((4-(6-(((10a*R*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (320 mg, 0.487 mmol) as a semisolid. LCMS (Method B): Rt = 1.79 min, m/z = 658.3 $[M+H]^+$, 93.77%.

Step 7. 2-((4-(6-(((8R,10aR)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide and 2-((4-(6-(((8S,10aR)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-f][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-ethyl-5-fluoro-N-isopropylbenzamide



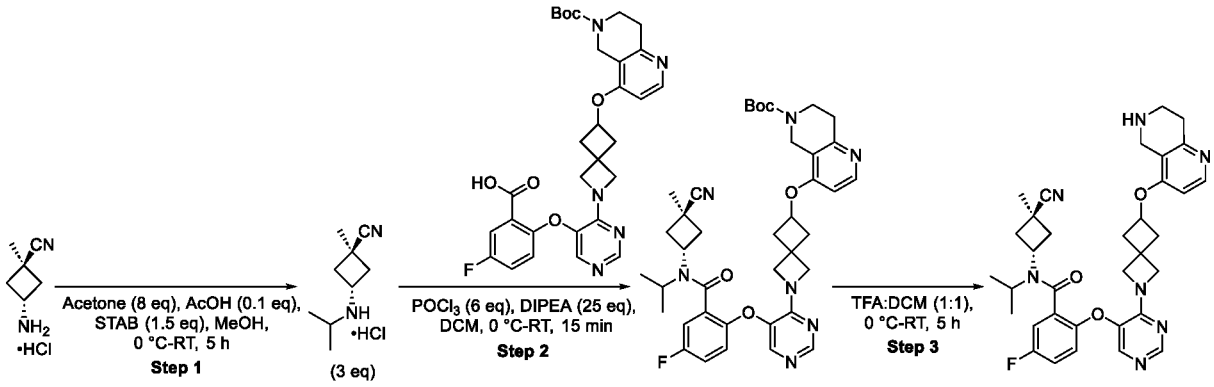
2-((4-(6-(((10a*R*)-8-(2-(Dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (320 mg) was purified by chiral Prep SFC (Method AV) to obtain both the diastereomers, 2-((4-(6-(((8*R*,10a*R*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (142.99 mg, 20.30% yield) and 2-((4-(6-(((8*S*,10a*R*)-8-(2-(dimethylamino)ethyl)-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*f*][1,6]naphthyridin-1-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (54.89 mg, 7.79% yield) as solids.

Isomer 1. 8.30 - 8.26 (m, 1H), 8.17 - 8.14 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.11 - 7.01 (m, 1H), 6.70 - 6.65 (m, 1H), 4.79 - 4.69 (m, 1H), 4.48 - 4.05 (m, 4H), 3.81 - 3.69 (m, 1H), 3.45 - 3.37 (m, 1H), 3.27 - 3.20 (m, 1H), 3.19 - 3.10 (m, 1H), 3.07 - 2.98 (m, 1H), 2.93 - 2.85 (m, 1H), 2.84 - 2.72 (m, 4H), 2.65 - 2.55 (m, 1H), 2.42 - 2.35 (m, 1H), 2.31 - 2.18 (m, 4H), 2.12 (s, 6H), 1.94 - 1.84 (m, 1H), 1.74 - 1.63 (m, 1H), 1.51 - - 1.29 (m, 3H), 1.22 -

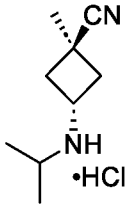
0.97 (m, 9H); LCMS (Method L): Rt = 1.52 min, m/z = 658.5 $[M+H]^+$; HPLC (Method G): Rt = 4.79 min, 99.54%; Chiral SFC (Method AAAD): Rt = 2.90 min, 99.69%.

Isomer 2. 8.31 - 8.26 (m, 1H), 8.18 - 8.14 (m, 1H), 7.76 - 7.66 (m, 1H), 7.33 - 7.22 (m, 2H), 7.10 - 7.01 (m, 1H), 6.67 - 6.61 (m, 1H), 4.78 - 4.68 (m, 1H), 4.47 - 4.06 (m, 4H), 3.80 - 3.70 (m, 1H), 3.44 - 3.37 (m, 1H), 3.27 - 3.21 (m, 2H), 3.19 - 3.12 (m, 1H), 3.04 - 2.92 (m, 1H), 2.82 - 2.71 (m, 4H), 2.45 - 2.37 (m, 2H), 2.33 - 2.17 (m, 4H), 2.13 (s, 6H), 1.94 - 1.80 (m, 2H), 1.51 - 1.29 (m, 3H), 1.22 - 0.96 (m, 9H); LCMS (Method L): Rt = 1.56 min, m/z = 658.5 $[M+H]^+$; HPLC (Method G): Rt = 4.82 min, 99.53%; Chiral SFC (Method AAAD): Rt = 5.52 min, 99.18%.

Example 450. ***N*-((1*r*,3*r*)-3-Cyano-3-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 450)



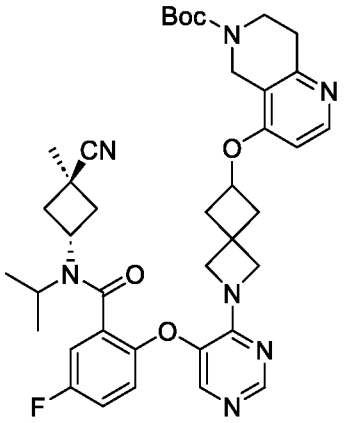
Step 1. (1r,3r)-3-(Isopropylamino)-1-methylcyclobutane-1-carbonitrile hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 436, step 1, starting with 1 equivalent of (1*r*,3*r*)-3-amino-1-methylcyclobutane-1-carbonitrile hydrochloride and 8 equivalents of acetone, except that 0.1 equivalent of AcOH and 1.5 equivalents of STAB were used, and MeOH was used as solvent. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with EtOAc. The filtrate was acidified with HCl (4M in 1,4 dioxane), and the mixture was concentrated under reduced pressure to obtain crude (1*r*,3*r*)-3-(isopropylamino)-1-methylcyclobutane-1-carbonitrile hydrochloride as a semi solid. This material was used without further purification.

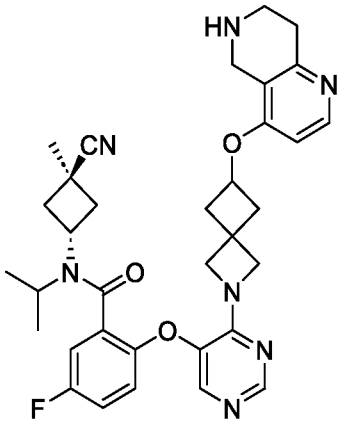
Yield: 93% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (br s, 2H), 4.01 - 3.88 (m, 1H), 3.24 - 3.12 (m, 1H), 2.79 - 2.70 (m, 2H), 2.69 - 2.58 (m, 2H), 1.53 (s, 3H), 1.22 (d, J = 6.5 Hz, 6H).

Step 2. tert-Butyl 4-((2-(5-(2-(((1r,3r)-3-cyano-3-methylcyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



In a 25 mL round bottom flask under a nitrogen atmosphere, 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid (210 mg, 0.364 mmol) was added in DCM (2.0 mL). To this solution, (1*r*,3*r*)-3-(isopropylamino)-1-methylcyclobutane-1-carbonitrile hydrochloride (206 mg, 1.091 mmol), DIPEA (1.587 mL, 9.09 mmol) and $POCl_3$ (0.203 mL, 2.181 mmol) were added 0 °C. The reaction was stirred at RT for 15 min. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (10 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(5-(2-(((1*r*,3*r*)-3-cyano-3-methylcyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 38.0% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.23 (d, J = 5.6 Hz, 1H), 7.88 - 7.61 (m, 1H), 7.37 - 7.19 (m, 2H), 7.16 - 7.03 (m, 1H), 6.73 (d, J = 5.8 Hz, 1H), 4.77 (quin, J = 6.5 Hz, 1H), 4.36 (s, 2H), 4.32 - 4.07 (m, 5H), 3.81 - 3.66 (m, 1H), 3.61 (br t, J = 5.7 Hz, 2H), 3.29 - 3.19 (m, 1H), 3.00 – 3.10 (m, 1H), 2.86 - 2.74 (m, 4H), 2.67 - 2.56 (m, 2H), 2.32 - 2.23 (m, 2H), 1.57 (s, 3H), 1.43 (s, 9H), 1.30 - 0.93 (m, 6H); LCMS (Method G): Rt = 2.13 min, m/z = 712.2 $[M+H]^+$, 98.27%.

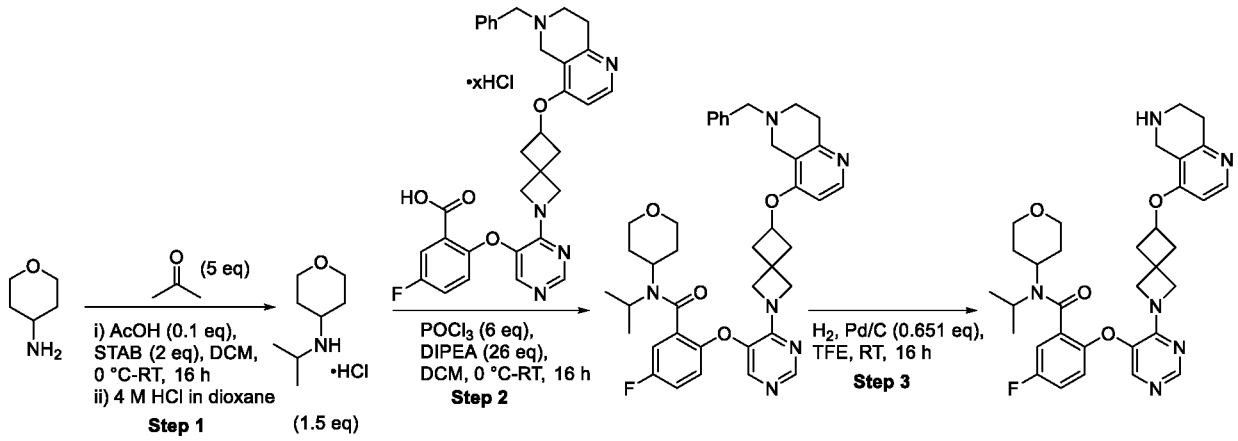
Step 3. N-((1r,3r)-3-Cyano-3-methylcyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



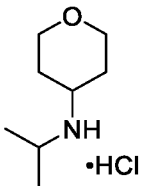
In a 8 mL pressure vial, *tert*-butyl 4-((2-(5-(2-(((1*r*,3*r*)-3-cyano-3-methylcyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (90 mg, 0.126 mmol) was added in DCM (0.9 mL). To this solution, TFA (0.9 mL, 0.126 mmol) was added at 0 °C and the reaction was stirred at RT for 2 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure and the crude was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-((1*r*,3*r*)-3-cyano-3-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (37 mg, 47.3% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.16 (d, *J* = 5.6 Hz, 1H), 7.81 - 7.61 (m, 1H), 7.37 - 7.21 (m, 2H), 7.16 - 7.02 (m, 1H), 6.64 (d, *J* = 5.6 Hz, 1H), 4.72 (quin, *J* = 6.6 Hz, 1H), 4.35 - 4.06 (m, 5H), 3.80 - 3.63 (m, 3H), 3.29 - 3.19 (m, 1H), 3.12 – 3.01 (m, 1H), 2.95 (t, *J* = 5.8 Hz, 2H), 2.84 - 2.73 (m, 2H), 2.71 - 2.56 (m, 5H), 2.30 - 2.18 (m, 2H), 1.62 - 1.42 (m, 3H), 1.31 - 0.94 (m, 6H); LCMS (Method G): Rt = 1.54 min, m/z = 612.1 $[M+H]^+$; HPLC (Method G): Rt = 4.94 min, 98.75%.

Note: A trace of TFA was observed in the ^{19}F NMR spectrum.

Example 451. 5-Fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide (Compound No. 451)

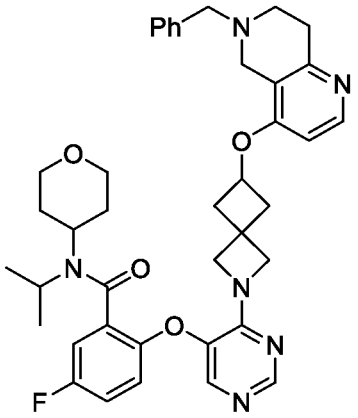


Step 1. N-Isopropyltetrahydro-2H-pyran-4-amine hydrochloride



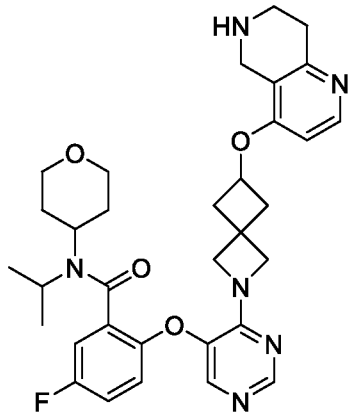
In a dried, round bottom flask under a nitrogen atmosphere, tetrahydro-2*H*-pyran-4-amine (2 g, 19.77 mmol) was dissolved in DCM (20 mL). To this solution, acetone (7.26 mL, 99 mmol) and acetic acid (0.113 mL, 1.977 mmol) were added at 0 °C, and the reaction was stirred at RT for 1 h. Triacetoxyborohydride (8.38 g, 39.5 mmol) was added to this reaction mixture at 0 °C, and the reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with $NaHCO_3$ (20 mL), and the mixture was extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure to afford crude *N*-isopropyltetrahydro-2*H*-pyran-4-amine (2.5 g, 88% yield) as a liquid. 4M HCl in 1,4-dioxane (4.71 mL, 18.85 mmol) was added to the crude *N*-isopropyltetrahydro-2*H*-pyran-4-amine (0.54 g, 3.77 mmol) at 0 °C, and the mixture was stirred at RT for 1 h. The solution was concentrated under reduced pressure. The crude was triturated with EtOAc (2 x 50 mL), and the organic layer was decanted. The resulting solid was dried under reduced pressure to afford crude *N*-isopropyltetrahydro-2*H*-pyran-4-amine hydrochloride (0.34 g, 50.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (br s, 2H), 3.89 (br dd, J = 4.1, 11.4 Hz, 2H), 3.42 - 3.32 (m, 4H), 1.97 - 1.87 (m, 2H), 1.74 - 1.59 (m, 2H), 1.27 (d, J = 6.4 Hz, 6H). This material was used without further purification.

Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydro-2H-pyran-4-yl)benzamide



In a dried, 8 mL pressure vial, 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid (0.5 g, 0.881 mmol) and *N*-isopropyltetrahydro-2*H*-pyran-4-amine hydrochloride (0.237 g, 1.321 mmol) were combined in DCM (10 mL) under a nitrogen atmosphere. To this solution, DIPEA (4.00 mL, 22.90 mmol) was added, and then $POCl_3$ (0.493 mL, 5.29 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction was monitored by TLC (10% MeOH in DCM). The reaction was quenched with saturated aqueous sodium bicarbonate solution (20 mL) and the mixture was extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide (0.063 g, 10.32% yield). LCMS (Method G): Rt = 2.04 min, m/z = 693.2 $[M+H]^+$, 96.99%.

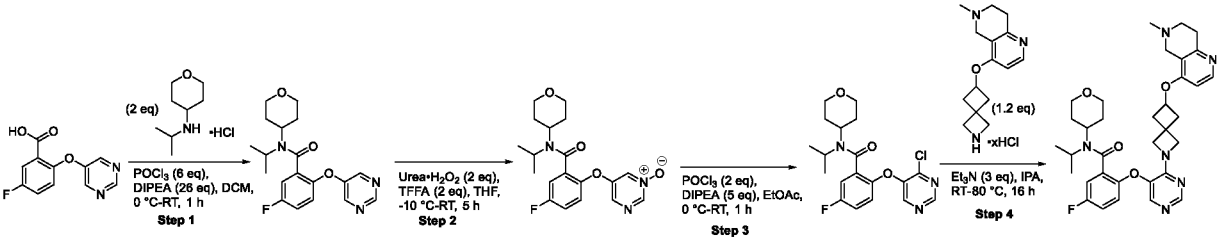
Step 3. 5-Fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydro-2H-pyran-4-yl)benzamide



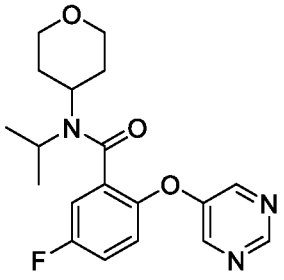
This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide, except that 0.651 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide as a solid.

Yield: 11.78%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 - 8.24 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.29 - 7.21 (m, 2H), 7.14 - 7.03 (m, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.73 (quin, J = 6.5 Hz, 1H), 4.31 - 4.09 (m, 4H), 3.92 - 3.72 (m, 3H), 3.70 (s, 2H), 3.59 - 3.48 (m, 1H), 3.43 - 3.35 (m, 2H), 3.14 - 3.05 (m, 1H), 2.95 (t, J = 5.8 Hz, 2H), 2.83 - 2.73 (m, 3H), 2.70 - 2.65 (m, 2H), 2.28 - 2.19 (m, 2H), 1.80 - 1.54 (m, 1H), 1.48 - 1.27 (m, 4H), 1.16 - 0.97 (m, 4H); LCMS (Method G): Rt = 1.55 min, m/z = 603.2 $[M+H]^+$; HPLC (Method G): Rt = 4.45 min, 97.67%.

Example 452. 5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide (Compound No. 452)



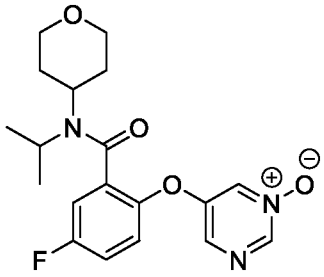
Step 1. 5-Fluoro-N-isopropyl-2-(pyrimidin-5-yloxy)-N-(tetrahydro-2H-pyran-4-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 451, step 2, starting with 2 equivalents of *N*-isopropyltetrahydro-2H-pyran-4-amine hydrochloride, except that 1 equivalent of 5-fluoro-2-(pyrimidin-5-yloxy)benzoic acid was used. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with aqueous sodium bicarbonate, and the mixture was extracted with DCM. The combined organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to afford 5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide as a solid.

Yield: 53.7%; LCMS (Method G) : Rt = 1.58 min, m/z = 360.1 $[M+H]^+$, 94.41%.

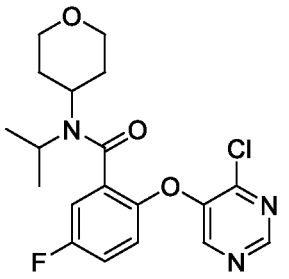
Step 2. 5-(4-Fluoro-2-(isopropyl(tetrahydro-2H-pyran-4-yl)carbamoyl)phenoxy)pyrimidine 1-oxide



This compound was synthesized following the procedure described for the synthesis of Intermediate 6, step 2 (Procedure 1), starting with 1 equivalent of 5-fluoro-*N*-isopropyl-2-(pyrimidin-5-yloxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide. After work-up, the filtrate was concentrated under reduced pressure to afford crude 5-(4-fluoro-2-(isopropyl(tetrahydro-2H-pyran-4-yl)carbamoyl)phenoxy)pyrimidine 1-oxide as a gummy solid. This material was used without further purification.

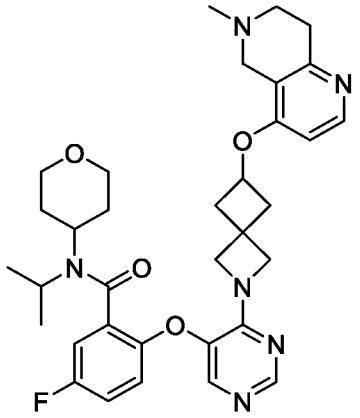
Yield: 99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 - 8.84 (m, 1H), 8.44 - 8.38 (m, 1H), 8.06 - 8.03 (m, 1H), 7.49 - 7.29 (m, 3H), 3.91 - 3.66 (m, 3H), 3.39 - 3.36 (m, 2H), 3.16 - 3.05 (m, 1H), 1.81 – 1.55 (m, 1H), 1.46 - 1.34 (m, 2H), 1.29 - 1.02 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.43 min, m/z = 376.1 $[M+H]^+$; 91.02%.

Step 3. 2-((4-Chloropyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(tetrahydro-2H-pyran-4-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Intermediate 6, step 3 (Procedure 1), starting with 1 equivalent of 5-(4-fluoro-2-(isopropyl(tetrahydro-2H-pyran-4-yl)carbamoyl)phenoxy)pyrimidine 1-oxide, except that 5 equivalents of DIEPA was used. The reaction progress was monitored by TLC (50% EtOAc in hexane). The crude product was purified by silica gel flash column chromatography using EtOAc in hexane (product eluted at 35% EtOAc in hexane) to obtain 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydro-2H-pyran-4-yl)benzamide as a solid.
Yield: 59.6%; LCMS (Method G) : Rt = 1.81 min, m/z = 394.0 $[M+H]^+$, 98.65%.

Step 4. 5-Fluoro-N-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydro-2H-pyran-4-yl)benzamide

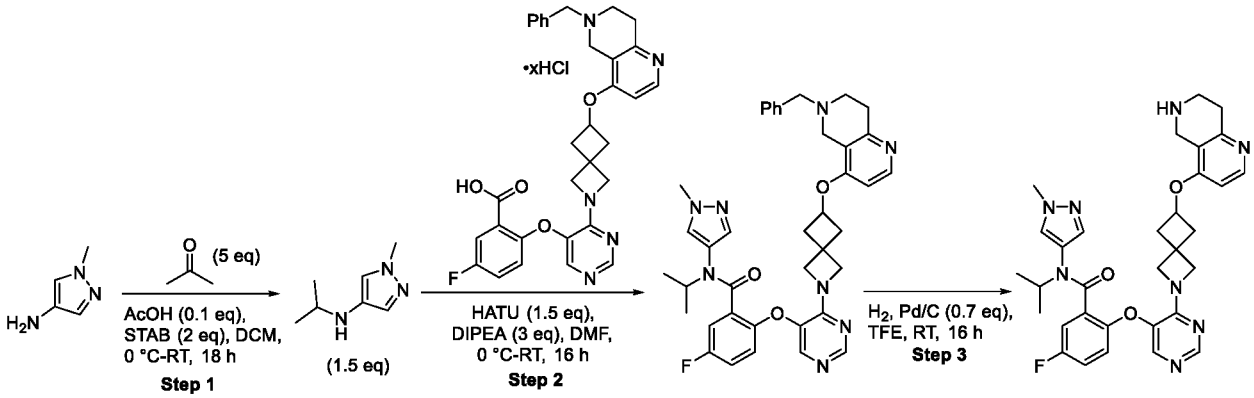


This compound was synthesized following the procedure described for the synthesis of Example 1, step 1, starting with 1 equivalent of 2-((4-chloropyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(tetrahydro-2H-pyran-4-yl)benzamide and 1.2 equivalents of 4-((2-azaspiro[3.3]heptan-6-yl)oxy)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine, except that 3 equivalents of TEA was used. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure, and saturated aqueous sodium bicarbonate solution was added. The mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The crude compound

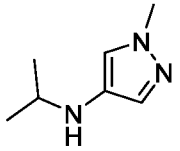
was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide as a solid.

Yield: 26.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 - 8.25 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.30 - 7.20 (m, 2H), 7.14 - 7.03 (m, 1H), 6.66 (d, J = 5.8 Hz, 1H), 4.75 (quin, J = 6.5 Hz, 1H), 4.35 - 4.07 (m, 4H), 3.92 - 3.49 (m, 3H), 3.44 - 3.35 (m, 4H), 3.17 - 3.05 (m, 1H), 2.84 - 2.73 (m, 5H), 2.66 - 2.61 (m, 2H), 2.37 (s, 3H), 2.30 - 2.22 (m, 2H), 1.79 - 1.59 (m, 1H), 1.49 - 1.27 (m, 4H), 1.15 - 0.98 (m, 4H); LCMS (Method G): Rt = 1.68 min, m/z = 617.2 $[M+H]^+$; HPLC (Method G): Rt = 4.93 min, 99.56%.

Example 453. 5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 453)



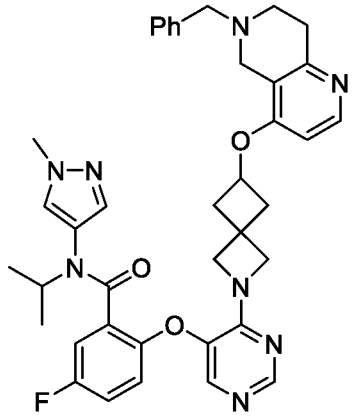
Step 1. N-Isopropyl-1-methyl-1H-pyrazol-4-amine



This compound was synthesized following the procedure described for the synthesis of Example 436, step 1, starting with 1 equivalent of 1-methyl-1H-pyrazol-4-amine and 5 equivalents of acetone, except that 0.1 equivalent of AcOH was used, and DCM was used as a solvent. After work-up, the crude product was purified by silica gel flash column chromatography using MeOH in DCM (product was eluted in 5% MeOH in DCM) to obtain *N*-isopropyl-1-methyl-1H-pyrazol-4-amine as a liquid.

Yield: 36.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.02 (d, J = 0.8 Hz, 1H), 6.91 (d, J = 0.8 Hz, 1H), 4.77 - 4.23 (m, 1H), 3.68 (s, 3H), 3.08 (spt, J = 6.3 Hz, 1H), 1.06 (d, J = 6.3 Hz, 6H); LCMS (Method G): Rt = 1.13 min, m/z = 140.1 $[M+H]^+$, 95.66%.

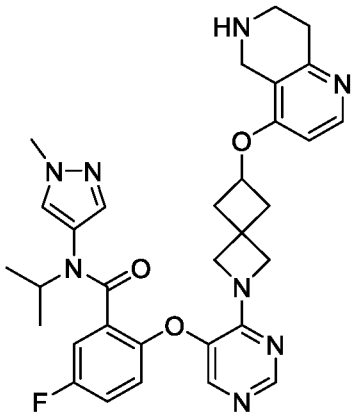
Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(1-methyl-1H-pyrazol-4-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 434, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl, except that 1.5 equivalents of *N*-isopropyl-1-methyl-1H-pyrazol-4-amine and 3 equivalents of DIPEA were used. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to afford 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)benzamide as a solid.

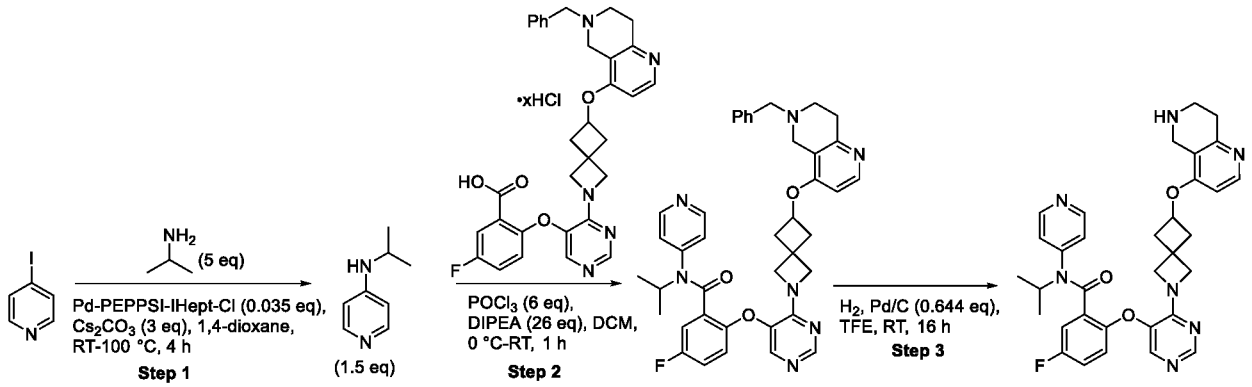
Yield: 28.26%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.62 (s, 1H), 7.47 (s, 1H), 7.38 - 7.32 (m, 4H), 7.31 - 7.25 (m, 1H), 7.24 - 7.19 (m, 2H), 7.05 (dt, J = 3.1, 8.6 Hz, 1H), 6.77 (dd, J = 4.4, 9.0 Hz, 1H), 6.68 (d, J = 5.6 Hz, 1H), 4.90 - 4.80 (m, 1H), 4.73 (quin, J = 6.7 Hz, 1H), 4.21 (s, 2H), 4.14 (s, 2H), 3.72 - 3.67 (m, 5H), 3.48 (s, 2H), 2.85 - 2.75 (m, 4H), 2.69 (br t, J = 5.9 Hz, 2H), 2.29 - 2.18 (m, 2H), 1.02 (d, J = 6.6 Hz, 6H); LCMS (Method G): Rt = 1.95 min, m/z = 689.1 $[M+H]^+$, 99.92%.

Step 3. 5-Fluoro-N-isopropyl-N-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

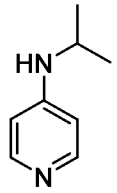


This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)benzamide, except that 0.7 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilzed to afford 5-fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.
Yield: 79%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.62 (s, 1H), 7.47 (s, 1H), 7.24 - 7.18 (m, 2H), 7.06 (dt, J = 3.1, 8.6 Hz, 1H), 6.78 (dd, J = 4.3, 9.0 Hz, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.92 - 4.78 (m, 1H), 4.74 (quin, J = 6.7 Hz, 1H), 4.22 (br s, 2H), 4.16 (br s, 2H), 3.70 (s, 5H), 2.95 (br t, J = 5.6 Hz, 2H), 2.86 - 2.75 (m, 2H), 2.72 - 2.65 (m, 2H), 2.32 - 2.20 (m, 2H), 1.03 (br d, J = 6.6 Hz, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.48 min, m/z = 599.2 $[M+H]^+$; HPLC (Method G): Rt = 4.15 min, 99.08%.

Example 454. 5-Fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 454)

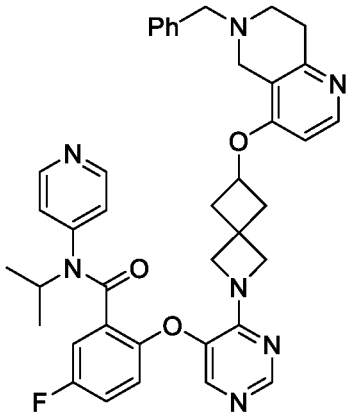


Step 1. N-Isopropylpyridin-4-amine



In a pressure vial, 4-iodopyridine (1 g, 4.88 mmol) and isopropylamine (2.120 mL, 24.39 mmol) were combined in 1,4-dioxane (20 mL) at RT. To this solution, Pd-PEPPSI-IHept-Cl (0.166 g, 0.244 mmol) and Cs_2CO_3 (4.77 g, 14.63 mmol) were added at RT. The reaction mixture was degassed with nitrogen for 15 min, then the reaction was stirred at 100 °C for 4 h. The reaction progress was monitored by LCMS. The reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 50 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *N*-isopropylpyridin-4-amine (700 mg, quantitative yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 - 7.94 (m, 2H), 6.46 - 6.42 (m, 2H), 6.32 (br d, J = 7.5 Hz, 1H), 3.65 - 3.53 (m, 1H), 1.13 (d, J = 6.3 Hz, 6H); LCMS (Method G): Rt = 1.08 min, m/z = 137.0 $[M+H]^+$, 95.99%.

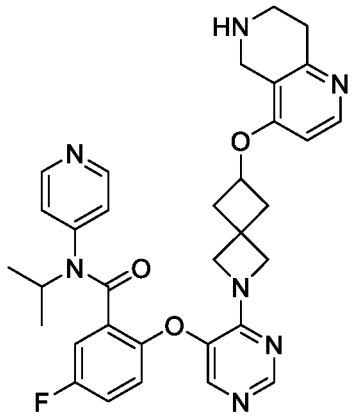
Step 2. 2-((4-(6-((6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropyl-N-(pyridin-4-yl)benzamide



This compound was synthesized following the procedure described for the synthesis of Example 451, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid xHCl, except that 1.5 equivalents of *N*-isopropylpyridin-4-amine was used. The crude was purified by silica gel flash column chromatography using EtOAc in hexane, and then with 1% TEA in MeOH in DCM (product was eluted in 10% MeOH in DCM (1% TEA)). The product was impure. Therefore, the product was re-purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)benzamide as a solid.

Yield: 16.80%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (br d, J = 4.9 Hz, 2H), 8.33 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.54 - 7.43 (m, 1H), 7.41 - 7.32 (m, 5H), 7.28 - 7.24 (m, 3H), 7.13 - 7.02 (m, 1H), 6.78 - 6.70 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.86 - 4.67 (m, 2H), 4.20 (s, 2H), 4.16 - 4.11 (m, 2H), 3.69 (s, 2H), 3.48 (s, 2H), 2.85 - 2.74 (m, 4H), 2.72 - 2.66 (m, 2H), 2.26 - 2.16 (m, 2H), 1.14 (br d, J = 6.6 Hz, 6H); LCMS (Method G): Rt = 1.95 min, m/z = 686.2 $[M+H]^+$, 90.19%.

Step 3. 5-Fluoro-N-isopropyl-N-(pyridin-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

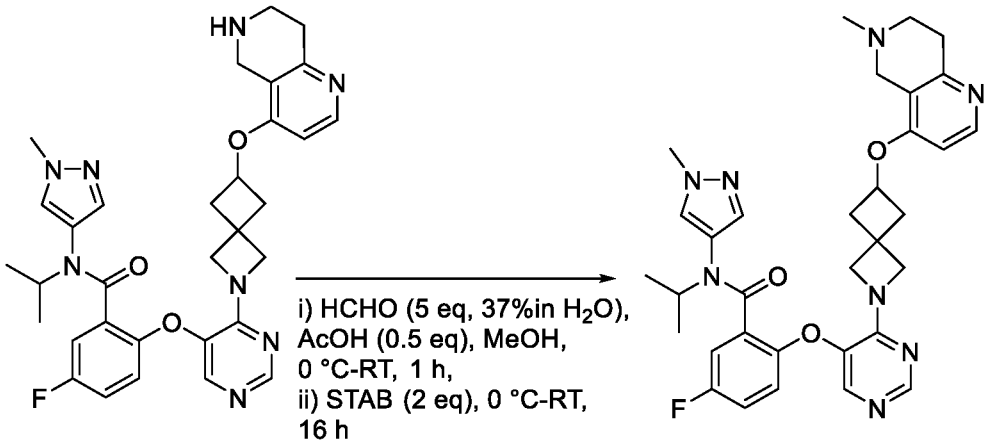


This compound was synthesized following the procedure described for the synthesis of Example 311, step 2, starting with 1 equivalent of 2-((4-(6-((6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)benzamide, except that 0.644 equivalent of Pd/C was used. After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH. The filtrate was concentrated under reduced pressure to afford crude 5-fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide.

Yield: 99.20%; LCMS (Method G): Rt = 1.55 min, m/z = 596.3 $[M+H]^+$; HPLC (Method G): Rt = 4.25 min, 99.52%.

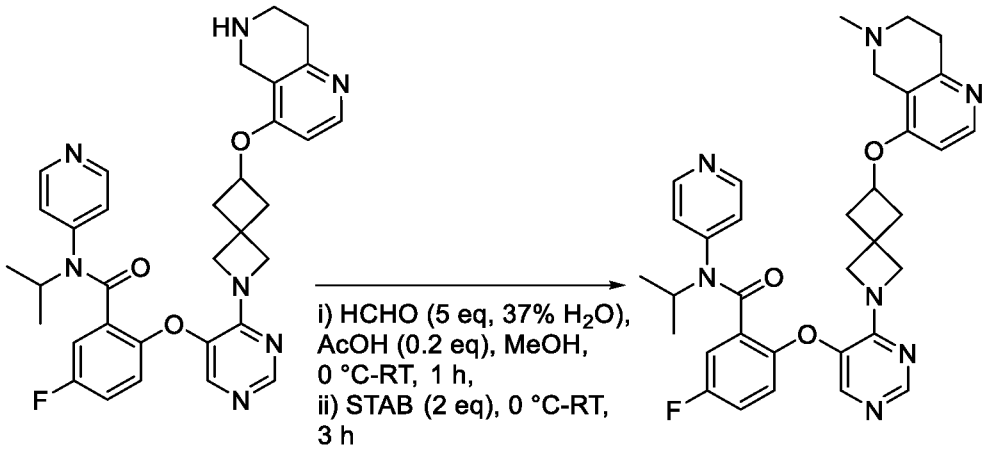
A portion of this material (50 mg) was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The product fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (26.33 mg, 10.44% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (br d, J = 4.6 Hz, 2H), 8.33 (s, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.47 (br s, 1H), 7.36 (br d, J = 4.9 Hz, 1H), 7.29 - 7.23 (m, 2H), 7.09 (br s, 1H), 6.82 - 6.71 (m, 1H), 6.65 (d, J = 5.6 Hz, 1H), 4.86 - 4.69 (m, 2H), 4.21 (s, 2H), 4.15 (s, 2H), 3.70 (s, 2H), 2.95 (br t, J = 5.4 Hz, 2H), 2.84 - 2.76 (m, 2H), 2.71 - 2.64 (m, 2H), 2.30 - 2.21 (m, 2H), 1.14 (br d, J = 6.6 Hz, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.50 min, m/z = 596.1 $[M+H]^+$; HPLC (Method G): Rt = 4.21 min, 99.84%.

Example 455. 5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 455)



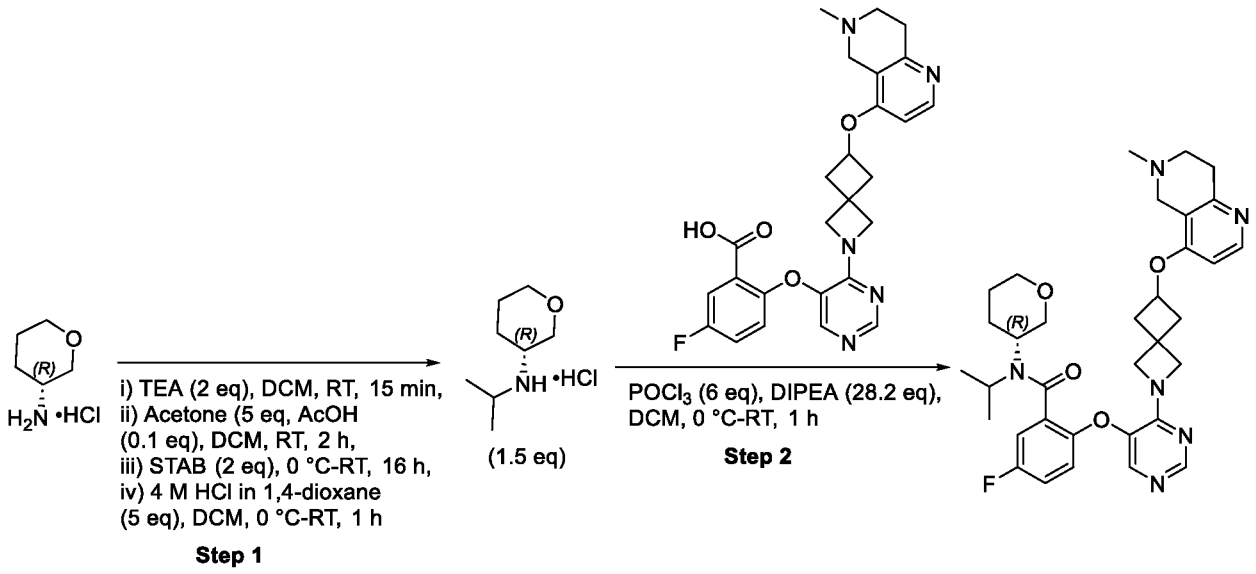
This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 5 equivalents of formaldehyde (37% in H_2O), except that 1 equivalent of 5-fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, 0.5 equivalent of AcOH and 2 equivalents of STAB were used, and MeOH was used as solvent. The reaction was concentrated under reduced pressure and the reaction was quenched with saturated aqueous sodium bicarbonate, and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-*N*-(1-methyl-1H-pyrazol-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Combined yield: 77.97%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.63 (s, 1H), 7.48 (s, 1H), 7.24 - 7.19 (m, 2H), 7.06 (dt, J = 3.2, 8.6 Hz, 1H), 6.77 (dd, J = 4.3, 9.1 Hz, 1H), 6.68 (d, J = 5.8 Hz, 1H), 4.91 - 4.80 (m, 1H), 4.76 (quin, J = 6.8 Hz, 1H), 4.22 (s, 2H), 4.16 (s, 2H), 3.70 (s, 3H), 3.37 (s, 2H), 2.84 - 2.76 (m, 4H), 2.63 (br t, J = 5.8 Hz, 2H), 2.37 (s, 3H), 2.31 - 2.24 (m, 2H), 1.03 (d, J = 6.8 Hz, 6H); LCMS (Method G): Rt = 1.60 min, m/z = 613.2 $[M+H]^+$; HPLC (Method G): Rt = 4.67 min, 99.44%.

Example 456. 5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(pyridin-4-yl)benzamide (Compound No. 456)

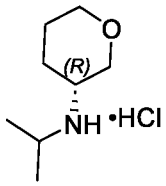


This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 5 equivalents of formaldehyde (37% in H_2O), except that 1 equivalent of 5-fluoro-*N*-isopropyl-*N*-(pyridin-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, 0.2 equivalent of AcOH and 2 equivalents of STAB was used, and MeOH was used as a solvent. The reaction was quenched with saturated aqueous sodium bicarbonate, and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(pyridin-4-yl)benzamide as a solid. Yield: 28.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (br d, J = 4.4 Hz, 2H), 8.33 (s, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.40 - 7.32 (m, 1H), 7.26 (d, J = 6.0 Hz, 2H), 7.15 - 7.04 (m, 1H), 6.79 - 6.70 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.86 - 4.70 (m, 2H), 4.21 (s, 2H), 4.15 (s, 2H), 3.37 (br s, 2H), 2.84 - 2.76 (m, 4H), 2.63 (br t, J = 5.8 Hz, 2H), 2.37 (s, 3H), 2.30 - 2.24 (m, 2H), 1.15 (br d, J = 6.8 Hz, 6H); LCMS (Method G): Rt = 1.62 min, m/z = 610.1 $[M+H]^+$; HPLC (Method G): Rt = 4.71 min, 99.61%.

Example 457. (*R*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-3-yl)benzamide (Compound No. 457)



Step 1. (R)-N-Isopropyltetrahydro-2H-pyran-3-amine hydrochloride

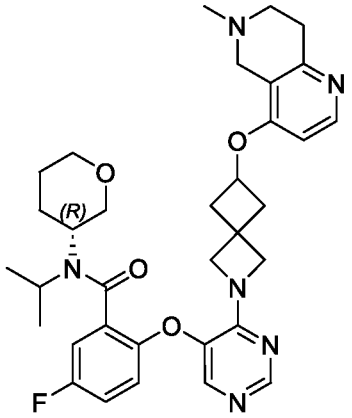


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*R*)-tetrahydro-2H-pyran-3-amine hydrochloride and 5 equivalents of acetone, except that 0.1 equivalent of AcOH and 2 equivalents of STAB were used. DCM was used as a solvent. The reaction was monitored by TLC (10 % MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using MeOH in DCM (product eluted at 4% MeOH in DCM) to obtain (*R*)-*N*-isopropyltetrahydro-2H-pyran-3-amine as a liquid. ^{1}H NMR showed the presence of acetic acid. To remove the acetic acid, the product was dissolved in DCM, 4 M HCl in 1,4-dioxane was added to this solution at 0 °C, and the solution was stirred at RT for 1 h. The reaction was concentrated under reduced pressure. The crude was triturated with EtOAc, the organic layer was decanted, and the solid was dried under vacuum to afford (*R*)-*N*-isopropyltetrahydro-2H-pyran-3-amine hydrochloride as a solid.

Yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 - 8.83 (m, 2H), 3.97 (dd, J = 2.3, 11.3 Hz, 1H), 3.72 (td, J = 3.8, 11.1 Hz, 1H), 3.51 (dd, J = 8.5, 11.3 Hz, 1H), 3.40 - 3.32 (m, 2H), 3.25 - 3.15 (m, 1H), 2.10 - 2.01 (m, 1H), 1.79 - 1.67 (m, 2H), 1.60 - 1.48 (m, 1H), 1.30 - 1.24 (m, 6H).

Note: ^{1}HNMR showed triethylamine hydrochloride salt impurity along with the product.

Step 2. (R)-5-Fluoro-N-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydro-2H-pyran-3-yl)benzamide

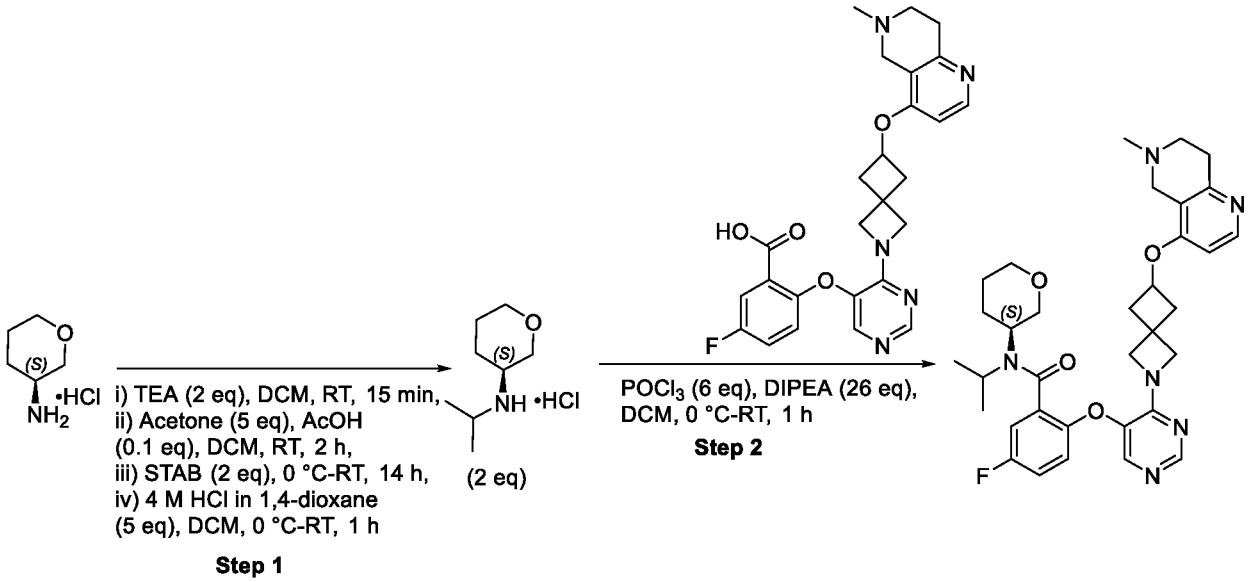


This compound was synthesized following the procedure described for the synthesis of Example 450, step 2, starting with 1 equivalent of 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid and 1.5 equivalents of 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid, except that 28.2 equivalents of DIPEA was used. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with saturated sodium bicarbonate solution and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN).

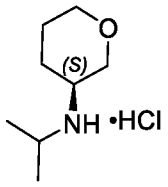
The product fractions were concentrated under reduced pressure and lyophilized to afford (*R*)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-3-yl)benzamide as a solid.

Yield: 21.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.75 - 7.64 (m, 1H), 7.35 - 7.20 (m, 2H), 7.13 - 6.99 (m, 1H), 6.66 (br d, J = 5.4 Hz, 1H), 4.75 (quin, J = 6.7 Hz, 1H), 4.33 - 4.09 (m, 5H), 3.81 - 3.57 (m, 3H), 3.53 - 3.41 (m, 1H), 3.37 (br s, 2H), 3.28 - 3.14 (m, 2H), 2.85 - 2.73 (m, 4H), 2.63 (br t, J = 5.7 Hz, 2H), 2.37 (s, 3H), 2.29 - 2.25 (m, 2H), 1.86 - 1.48 (m, 3H), 1.47 - 1.27 (m, 2H), 1.13 - 0.96 (m, 4H); LCMS (Method G): Rt = 1.73 min, m/z = 617.1 $[M+H]^+$; HPLC (Method G): Rt = 5.11 min, 98.4%; Chiral SFC (Method H): Rt = 3.65 min, 100%.

Example 458. (*S*)-5-Fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-3-yl)benzamide (Compound No. 458)



Step 1. *(S)-N-Isopropyltetrahydro-2H-pyran-3-amine hydrochloride*

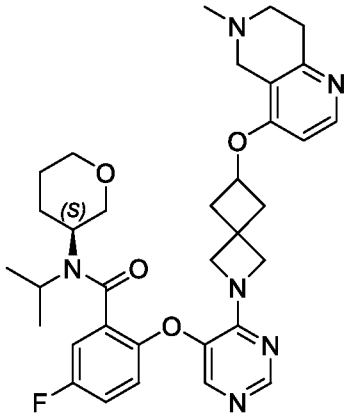


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*S*)-tetrahydro-2H-pyran-3-amine hydrochloride and 5 equivalents of acetone, except that 0.1 equivalent of AcOH and 2 equivalents of STAB were used, and DCM was used as a solvent. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with saturated sodium bicarbonate solution and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by neutral alumina flash column chromatography using MeOH in DCM (product eluted at 7% MeOH in DCM) to obtain (*S*)-*N*-isopropyltetrahydro-2H-pyran-3-amine as a liquid. ^{1}H NMR showed the presence of acetic acid. To remove the acetic acid, the product was dissolved in DCM, 4 M HCl in 1,4-dioxane was added to this solution at 0 °C, and the solution was stirred at RT for 1 h. The reaction was concentrated under reduced pressure. The crude was triturated with EtOAc, the organic layer was decanted, and the solid was dried under vacuum to afford (*S*)-*N*-isopropyltetrahydro-2H-pyran-3-amine hydrochloride as a solid.

Yield: 72.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 - 9.05 (m, 2H), 3.99 (dd, J = 2.3, 11.1 Hz, 1H), 3.73 (td, J = 3.5, 11.1 Hz, 1H), 3.52 (dd, J = 8.9, 11.1 Hz, 1H), 3.38 - 3.30 (m, 2H), 3.24 - 3.14 (m, 1H), 2.11 - 2.02 (m, 1H), 1.79 - 1.67 (m, 2H), 1.62 - 1.50 (m, 1H), 1.30 - 1.24 (m, 6H).

Note: ^{1}HNMR showed triethylamine hydrochloride salt impurity along with the product.

Step 2. (S)-5-Fluoro-N-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-N-(tetrahydro-2H-pyran-3-yl)benzamide



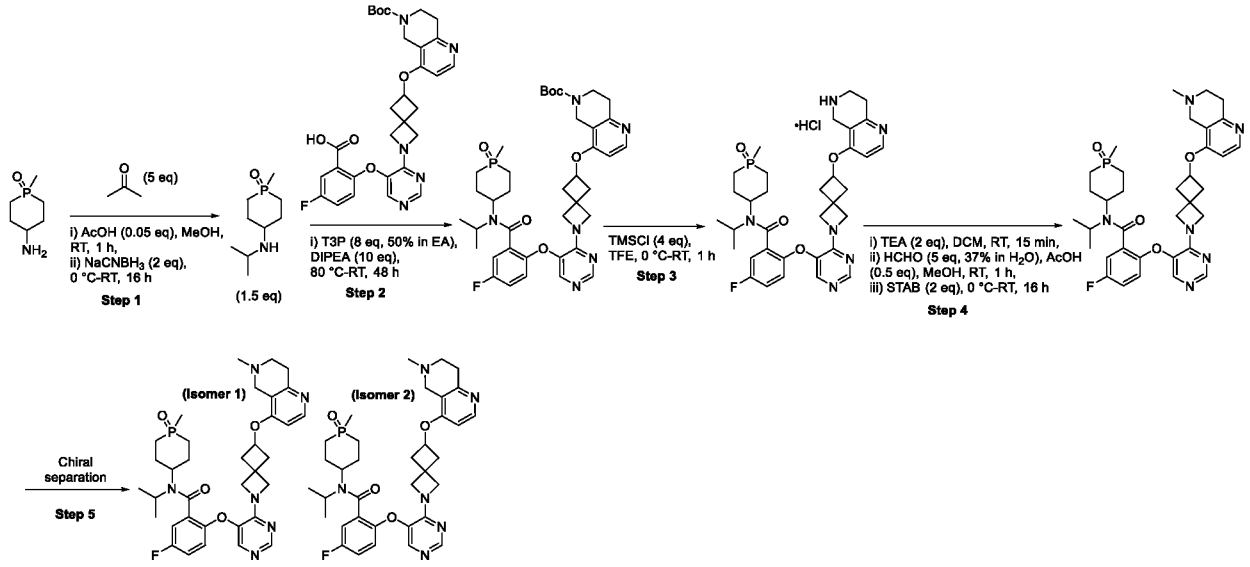
This compound was synthesized following the procedure described for the synthesis of Example 450, step 2, starting with 1 equivalent of 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid and 2 equivalents of (*S*)-*N*-isopropyltetrahydro-2H-pyran-3-amine hydrochloride, except that 26 equivalents of DIPEA was used. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with saturated aqueous sodium bicarbonate solution and the mixture was extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford (*S*)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-*N*-(tetrahydro-2H-pyran-3-yl)benzamide as a solid.

Yield: 13.64%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.27 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.75 - 7.64 (m, 1H), 7.35 - 7.19 (m, 2H), 7.14 - 6.99 (m, 1H), 6.66 (br d, J = 5.5 Hz, 1H), 4.75 (quin, J = 6.6 Hz, 1H), 4.33 - 4.08 (m, 5H), 3.82 - 3.57 (m, 3H), 3.54 - 3.41 (m, 1H), 3.37 (br s, 2H), 3.27 - 3.12 (m, 2H), 2.85 - 2.73 (m, 4H), 2.63 (br t, J = 5.8 Hz, 2H), 2.37

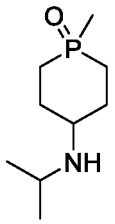
(s, 3H), 2.30 - 2.20 (m, 2H), 1.89 - 1.49 (m, 3H), 1.47 - 1.28 (m, 2H), 1.15 - 0.93 (m, 4H); LCMS (Method G): Rt = 1.73 min, m/z = 617.1 $[M+H]^+$; HPLC (Method G): Rt = 5.12 min, 98.39%; Chiral SFC (Method H): Rt = 3.49 min, 100%.

Example 459. (*E1*)-5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 459)

Example 460. (*E2*)-5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 460)



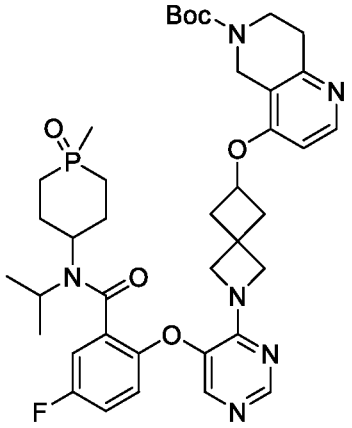
Step 1. (cis/trans)-4-(Isopropylamino)-1-methylphosphinane 1-oxide



To a stirred solution of (*cis/trans*)-4-amino-1-methylphosphinane 1-oxide (0.8 g, 5.44 mmol) and acetone (2.011 mL, 27.2 mmol) in MeOH (16 mL), AcOH (0.016 mL, 0.272 mmol) was added RT. The reaction was stirred at RT for 1 h. To this reaction mixture, $NaBH_3CN$ (0.683 g, 10.87 mmol) was added at 0 °C and the reaction was stirred at RT for 16 h. The reaction progress was monitored by TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure. The crude compound was purified by neutral alumina flash column chromatography using MeOH in DCM (product eluted at 9% MeOH in DCM) to obtain

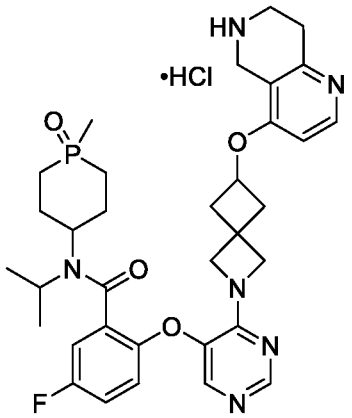
(*cis/trans*)-4-(isopropylamino)-1-methylphosphinane 1-oxide (550 mg, 50.0% yield) as a solid. LCMS-ELSD (Method G): Rt = 0.44 min, m/z = 190.1 $[M+H]^+$, 93.55%.

Step 2. (cis/trans)-tert-Butyl 4-((2-(5-(4-fluoro-2-(isopropyl(1-methyl-1-oxidophosphinan-4-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



To a stirred solution of *(cis/trans)*-2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid (590 mg, 1.021 mmol), (*cis/trans*)-4-(isopropylamino)-1-methylphosphinane 1-oxide (290 mg, 1.532 mmol) and DIPEA (1784 µL, 10.21 mmol), T3P (3171 µL, 8.17 mmol, 50% in EtOAc) was added at 0 °C. The reaction was stirred at 80 °C for 48 h. The reaction progress was monitored by LCMS and TLC (10% MeOH in DCM). The reaction was concentrated under reduced pressure and the crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to obtain *(cis/trans)-tert*-butyl 4-((2-(5-(4-fluoro-2-(isopropyl(1-methyl-1-oxidophosphinan-4-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (120 mg, 14.41% yield) as a solid. LCMS (Method B): Rt = 1.41 min, m/z = 749.2 $[M+H]^+$, 91.86%.

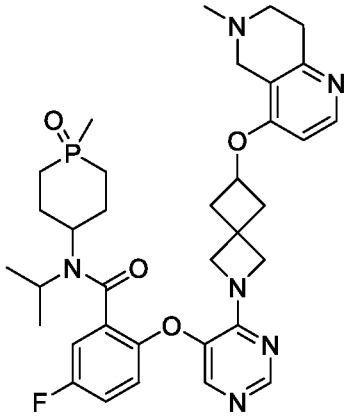
Step 3. (cis/trans)-5-Fluoro-N-isopropyl-N-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride



This compound was synthesized following the procedure described for the synthesis of Example 1, step 2, starting with 1 equivalent of *(cis/trans)-tert*-butyl 4-((2-(5-(4-fluoro-2-(isopropyl(1-methyl-1-oxidophosphinan-4-yl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. After completion, the reaction was concentrated under reduced pressure to obtain crude (*cis/trans*)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride as a solid. This material was used without further purification.

Yield: 92% yield; LCMS (Method G): Rt = 1.34 min, m/z = 649.1 $[M+H]^+$, 91.74%.

Step 4. (cis/trans)-5-Fluoro-N-isopropyl-N-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

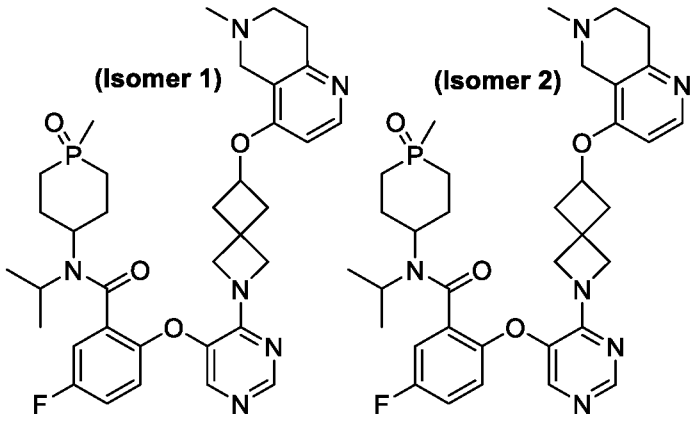


This compound was synthesized following the procedure described for the synthesis of Example 218, starting with 1 equivalent of (*cis/trans*)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide hydrochloride and 5 equivalents of formaldehyde (37% in H_2O), except that 0.5 equivalent of AcOH and 2 equivalents of STAB were used. After completion, the reaction was concentrated under reduced pressure. The

crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (60 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The pure fractions were concentrated under reduced pressure to afford (*cis/trans*)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 76%; LCMS (Method G): Rt = 1.45 min, m/z = 633.1 $[M+H]^+$; HPLC (Method G): Rt = 4.23 min, 88.31%; Chiral SFC (Method AAAE): Peak 1: Rt = 4.79 min, 38.45%; Peak 2: Rt = 8.15 min, 49.00%.

Step 5. (E1)-5-Fluoro-N-isopropyl-N-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide and (E2)-5-fluoro-N-isopropyl-N-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



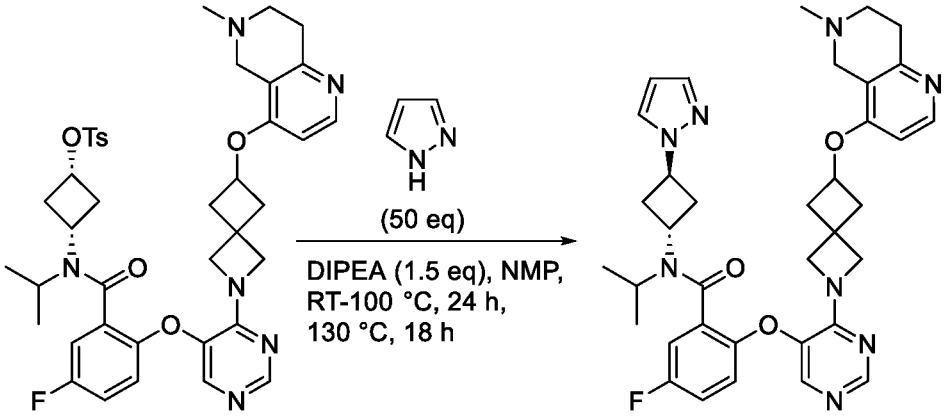
(*cis/trans*)-5-Fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (85 mg, 0.128 mmol) was purified by chiral Prep SFC (Method AW). The product fractions were concentrated under reduced pressure to obtain Isomer 1 (40 mg) and Isomer 2 (38 mg). Both the purified isomers showed impurities by HPLC. Therefore, both isomers were re-purified individually by reverse phase chromatography using a SiliCycle SiliaSep C18 column (12 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain (*E1*)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (19 mg, 22.08% yield) and (*E2*)-5-fluoro-*N*-isopropyl-*N*-(1-methyl-1-oxidophosphinan-4-yl)-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-

4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (24 mg, 27.5% yield) as solids.

Isomer 1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 - 8.26 (m, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.31 - 7.21 (m, 2H), 7.13 - 7.04 (m, 1H), 6.70 - 6.64 (m, 1H), 4.80 - 4.70 (m, 1H), 4.33 - 4.17 (m, 3H), 4.16 - 4.08 (m, 1H), 3.76 - 3.41 (m, 1H), 3.37 (s, 2H), 3.26 - 2.91 (m, 2H), 2.85 - 2.74 (m, 4H), 2.66 - 2.58 (m, 2H), 2.40 - 2.34 (m, 3H), 2.30 - 2.20 (m, 2H), 2.09 - 1.68 (m, 5H), 1.66 - 1.49 (m, 2H), 1.48 - 1.28 (m, 5H), 1.13 - 0.94 (m, 4H); LCMS (Method G): Rt = 1.47 min, m/z = 633.1 $[M+H]^+$; HPLC (Method G): Rt = 4.24 min, 98.80%; Chiral SFC (Method AAAE): Rt = 5.77 min, 100%.

Isomer 2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 - 8.24 (m, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.89 - 7.67 (m, 1H), 7.29 - 7.21 (m, 2H), 7.16 - 7.07 (m, 1H), 6.67 (d, J = 5.6 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.35 - 4.09 (m, 4H), 3.70 - 3.59 (m, 1H), 3.48 – 3.39 (m, 1H), 3.36 (br s, 2H), 2.86 - 2.74 (m, 5H), 2.66 - 2.60 (m, 2H), 2.38 - 2.35 (m, 3H), 2.30 - 2.20 (m, 2H), 1.99 - 1.52 (m, 7H), 1.48 - 1.28 (m, 5H), 1.14 - 0.93 (m, 4H); LCMS (Method G): Rt = 1.46 min, m/z = 633.1 $[M+H]^+$; HPLC (Method G): Rt = 4.23 min, 97.37%; Chiral SFC (Method AAAE): Rt = 10.00 min, 100%.

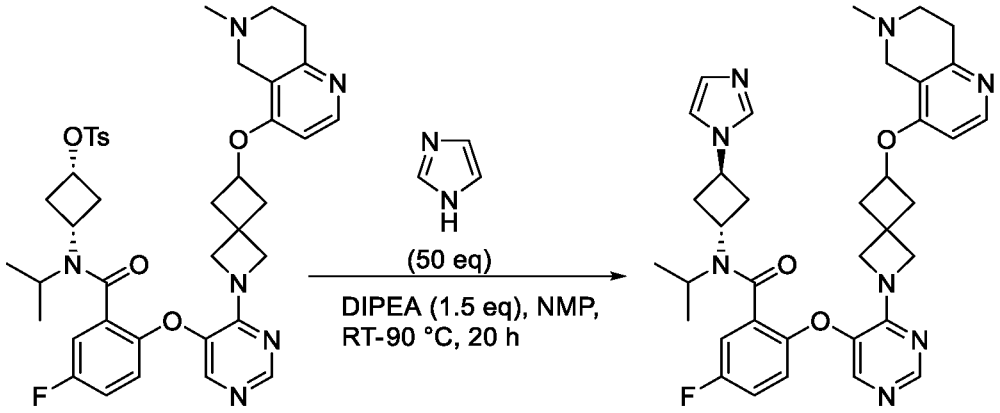
Example 461. ***N*-((1*r*,3*r*)-3-(1*H*-Pyrazol-1-yl)cyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 461)



In an 8 mL pressure vial, (1*s*,3*s*)-3-(5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamido)cyclobutyl 4-methylbenzenesulfonate (100 mg, 0.132 mmol) was dissolved in NMP (2 mL). To this solution, DIPEA (0.035 mL, 0.198 mmol), and 1*H*-pyrazole (450 mg, 6.61 mmol) were added at RT. The reaction was stirred at 100 °C for 24 h and continued at 130 °C for another 18 h. The progress of the reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was quenched with water (10

mL) and the mixture was extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine solution (10 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-((1*r*,3*r*)-3-(1H-pyrazol-1-yl)cyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (10 mg, 11.12% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 - 8.25 (m, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.88 - 7.66 (m, 2H), 7.54 - 7.40 (m, 1H), 7.37 (dd, J = 3.0, 8.1 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.12 - 7.01 (m, 1H), 6.71 - 6.59 (m, 1H), 6.28 - 6.14 (m, 1H), 5.36 - 5.19 (m, 1H), 4.84 - 4.62 (m, 2H), 4.45 - 4.08 (m, 5H), 3.94 - 3.67 (m, 1H), 3.36 (br s, 2H), 3.25 - 3.15 (m, 1H), 2.88 - 2.73 (m, 4H), 2.70 - 2.61 (m, 3H), 2.36 (s, 3H), 2.29 - 2.17 (m, 2H), 1.56 - 1.33 (m, 2H), 1.13 - 0.95 (m, 4H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.84 min, m/z = 653.2 $[M+H]^+$; HPLC (Method H): Rt = 9.04 min, 95.88%. Chiral SFC (Method J): Rt = 3.48 min, 100%.

Example 462. *N*-((1*r*,3*r*)-3-(1*H*-Imidazol-1-yl)cyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 462)

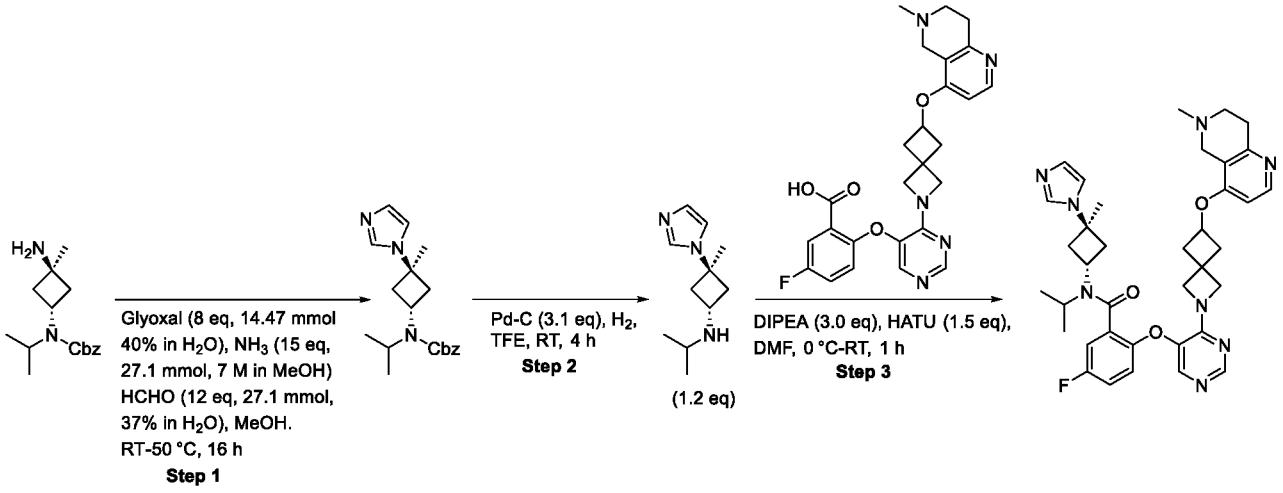


This compound was synthesized following the procedure described for the synthesis of Example 461, starting with 1 equivalent of (1*s*,3*s*)-3-(5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamido)cyclobutyl 4-methylbenzenesulfonate, and 50 equivalents of 1*H*-imidazole. The reaction was stirred at 90 °C for 20 h. The crude compound was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC

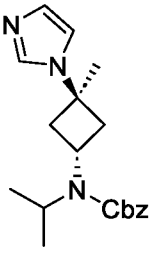
(Method AS) to obtain *N*-((1*r*,3*r*)-3-(1*H*-imidazol-1-yl)cyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 23.14%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.22 (m, 1H), 8.20 - 8.15 (m, 1H), 7.83 - 7.69 (m, 2H), 7.45 (s, 1H), 7.37 (dd, *J* = 2.9, 8.2 Hz, 1H), 7.31 - 7.24 (m, 1H), 7.08 (dd, *J* = 4.3, 9.1 Hz, 1H), 6.95 - 6.92 (m, 1H), 6.68 - 6.63 (m, 1H), 5.25 - 5.11 (m, 1H), 4.86 - 4.68 (m, 1H), 4.48 - 4.34 (m, 1H), 4.33 - 4.05 (m, 5H), 3.86 - 3.68 (m, 1H), 3.36 (br s, 2H), 3.25 - 3.17 (m, 1H), 2.85 - 2.73 (m, 5H), 2.66 - 2.58 (m, 2H), 2.36 (s, 3H), 2.35 - 2.32 (m, 1H), 2.30 - 2.20 (m, 2H), 1.55 - 0.91 (m, 6H); LCMS (Method G): Rt = 1.67 min, m/z = 653.2 [M+H]$^+$; HPLC (Method H): Rt = 8.28 min, 99.77%; Chiral SFC (Method AAAF) = 4.34 min; 100%.

Example 463. ***N*-((1*r*,3*r*)-3-(1*H*-Imidazol-1-yl)-3-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide** (Compound No. 463)



Step-1. Benzyl ((1r,3r)-3-(1H-imidazol-1-yl)-3-methylcyclobutyl)(isopropyl)carbamate



In a 100 mL round bottom flask under a nitrogen atmosphere, benzyl ((1*r*,3*r*)-3-amino-3-methylcyclobutyl)(isopropyl)carbamate (0.5 g, 1.809 mmol) and MeOH (10 mL), glyoxal (1.693 mL, 14.47 mmol, 40% in H_2O), formaldehyde (1.616 mL, 21.71 mmol, 37% in H_2O), and ammonia (3.88 mL, 27.1 mmol, 7 M in MeOH) were combined at RT. The reaction was

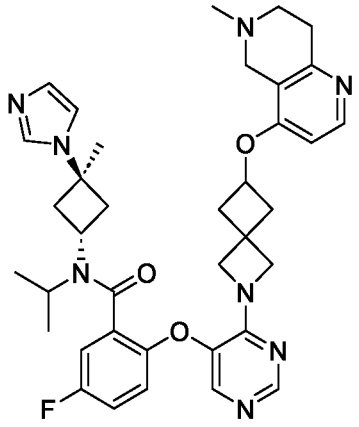
stirred at 50 °C for 16 h. The reaction was monitored by LCMS and TLC (5% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The reaction was diluted with water (20 mL) and the mixture was extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure to obtain benzyl ((1*r*,3*r*)-3-(1*H*-imidazol-1-yl)-3-methylcyclobutyl)(isopropyl)carbamate (400 mg, 66.2% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 1H), 7.41 - 7.38 (m, 4H), 7.38 – 7.31 (m, 1H), 7.31 (s, 1H), 6.93 (s, 1H), 5.11 (s, 2H), 4.13 - 3.97 (m, 2H), 2.84 - 2.75 (m, 2H), 2.74 - 2.70 (m, 2H), 1.48 - 1.39 (m, 3H), 1.11 (d, *J* = 6.9 Hz, 6H); LCMS (Method G): Rt = 1.94 min, m/z = 328.2 $[M+H]^+$, 98.62%.

Step-2. (1r,3r)-3-(1H-Imidazol-1-yl)-N-isopropyl-3-methylcyclobutan-1-amine



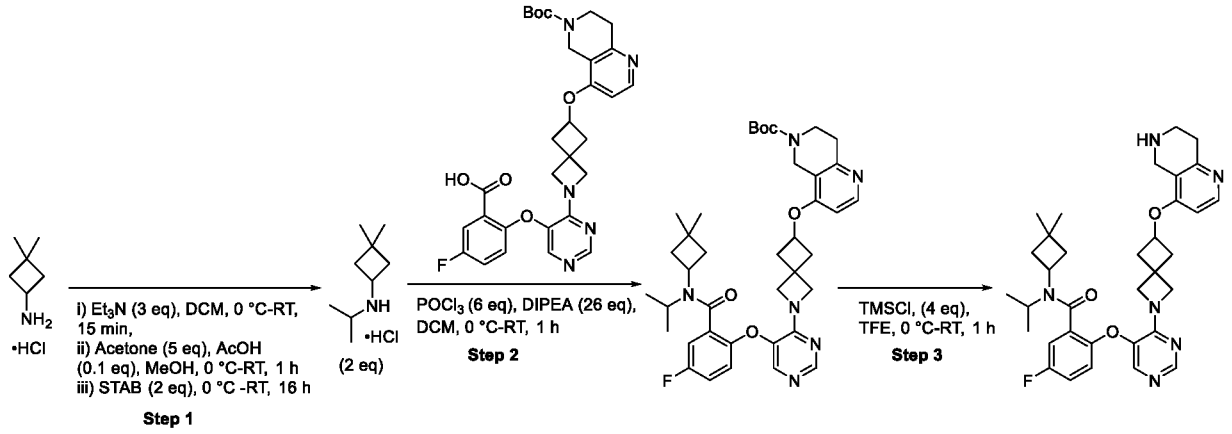
In a round bottom flask under a nitrogen atmosphere, benzyl ((1*r*,3*r*)-3-(1*H*-imidazol-1-yl)-3-methylcyclobutyl)(isopropyl)carbamate (400 mg, 1.222 mmol) was dissolved in TFE (5 mL). The resulting mixture was purged with nitrogen for 5 min. To this solution, Pd-C (403 mg, 3.79 mmol) was added. The reaction was stirred under a hydrogen atmosphere (balloon pressure) at RT for 4 h. The reaction was monitored by LCMS and TLC (5% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 30 mL). The filtrate was concentrated under reduced pressure to obtain crude (1*r*,3*r*)-3-(1*H*-imidazol-1-yl)-*N*-isopropyl-3-methylcyclobutan-1-amine (132 mg, 37.6% yield) as a sticky solid. This material was used without further purification. LCMS (Method G): Rt = 1.15 min, m/z = 194.1 $[M+H]^+$, 44.89%.

Step-3. N-((1r,3r)-3-(1H-Imidazol-1-yl)-3-methylcyclobutyl)-5-fluoro-N-isopropyl-2-((4-((6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide

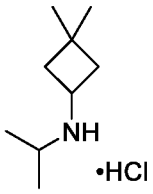


In a 20 mL pressure vial, 5-fluoro-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzoic acid (550 mg, 1.119 mmol) and (1*r*,3*r*)-3-(1*H*-imidazol-1-yl)-*N*-isopropyl-3-methylcyclobutan-1-amine (260 mg, 1.343 mmol) were dissolved in DMF (6 mL). To this mixture, DIPEA (0.585 mL, 3.36 mmol) and HATU (638 mg, 1.678 mmol) were added. The reaction was stirred at RT for 1 h. The progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN), then by Prep HPLC (Method-AS). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-((1*r*,3*r*)-3-(1*H*-imidazol-1-yl)-3-methylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid (69 mg, 9.24% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 - 8.24 (m, 1H), 8.22 - 8.14 (m, 1H), 7.88 (s, 1H), 7.80 - 7.64 (m, 1H), 7.44 - 7.14 (m, 3H), 7.12 - 7.03 (m, 1H), 6.97 - 6.85 (m, 1H), 6.72 - 6.62 (m, 1H), 4.80 - 4.70 (m, 1H), 4.36 - 4.09 (m, 4H), 4.06 - 3.67 (m, 2H), 3.48 - 3.38 (m, 1H), 3.36 (br s, 2H), 3.29 - 3.21 (m, 1H), 2.86 – 2.70 (m, 4H), 2.62 (br t, *J* = 5.8 Hz, 2H), 2.45 - 2.39 (m, 1H), 2.39 - 2.34 (m, 3H), 2.30 - 2.22 (m, 2H), 1.71 - 1.48 (m, 3H), 1.47 - 0.92 (m, 6H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.64 min, m/z = 667.2 $[M+H]^+$; HPLC (Method H): Rt = 8.51 min, 99.91%, Chiral HPLC (Method AJ): Rt = 4.30 min, 100%.

Example 464. *N*-(3,3-Dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 464)



Step 1. N-Isopropyl-3,3-dimethylcyclobutan-1-amine hydrochloride

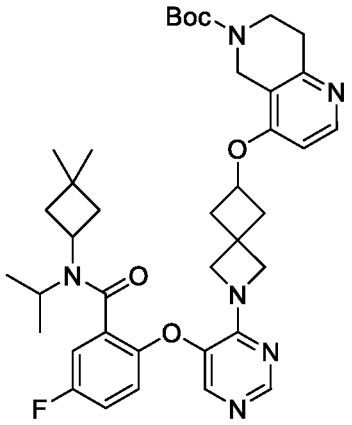


In a dried, 50 mL two-neck round bottom flask under a nitrogen atmosphere, 3,3-dimethylcyclobutan-1-amine hydrochloride (0.5 g, 3.69 mmol) was dissolved in DCM (5 mL). To this solution, TEA (1.541 mL, 11.06 mmol) was added, and the reaction was stirred at RT. After 15 min, the reaction was concentrated under reduced pressure and the residue was dissolved in MeOH (5 mL). To this reaction mixture, acetone (1.355 mL, 18.43 mmol) and AcOH (0.021 mL, 0.369 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h, then was re-cooled to 0 °C. Sodium triacetoxyborohydride (1.563 g, 7.37 mmol) was added, and the reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was filtered through a Celite® pad, and the pad was washed with MeOH (2 x 30 mL). To this filtrate, 4 M HCl in dioxane (4.61 mL, 18.43 mmol) was added at 0°C, and the mixture was stirred at RT for 1 h. The reaction was concentrated under reduced pressure to afford crude *N*-isopropyl-3,3-dimethylcyclobutan-1-amine hydrochloride (1.2 g) as a solid. This material was used without further purification.

LCMS-ELSD (Method J): Rt = 1.20 min, m/z = 142.2 $[M+H]^+$, 83.33%.

Note: Impurities were present in the product.

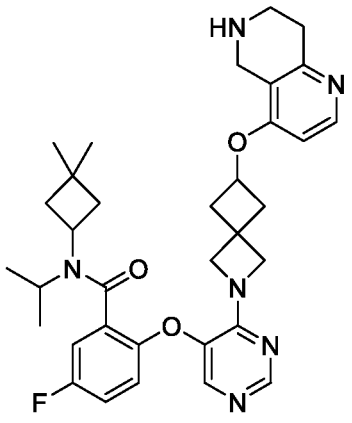
Step 2. tert-Butyl 4-((2-(5-(2-((3,3-dimethylcyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 450, step 2, starting with 1 equivalent of 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid and 2 equivalents of *N*-isopropyl-3,3-dimethylcyclobutan-1-amine hydrochloride, except that 26 equivalents of DIPEA was used. After completion, the reaction was quenched with 10% saturated sodium bicarbonate solution at 0 °C. The mixture was extracted with DCM, and the combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(5-(2-((3,3-dimethylcyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

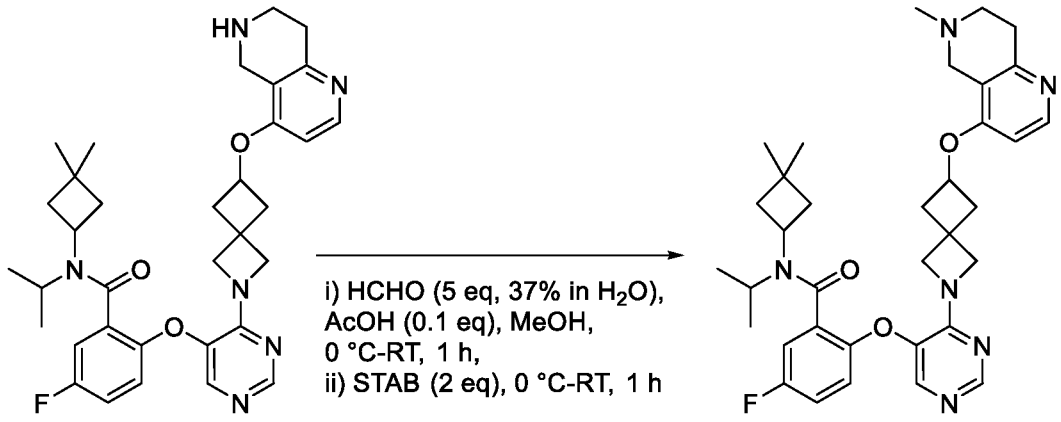
Yield: 24.53%; LCMS (Method G): Rt = 2.40 min, m/z = 701.2 $[M+H]^+$, 86.97%.

Step 3. N-(3,3-Dimethylcyclobutyl)-5-fluoro-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *tert*-butyl 4-((2-(5-(2-((3,3-dimethylcyclobutyl)(isopropyl)carbamoyl)-4-fluorophenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.9 g, 1.284 mmol) in TFE (18 mL), TMSCl (0.698 mL, 5.14 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h. The reaction progress was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The residue was dissolved in DCM (10 mL) and TEA (1 mL) was added at RT. The reaction was stirred at RT for 15 min, then was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-(3,3-dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (355 mg, 45.7% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.21 (m, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.33 - 7.04 (m, 3H), 6.63 (br d, J = 5.1 Hz, 1H), 4.72 (quin, J = 6.5 Hz, 1H), 4.36 - 4.09 (m, 4H), 4.03 - 3.85 (m, 1H), 3.77 - 3.62 (m, 3H), 2.94 (br t, J = 5.7 Hz, 2H), 2.83 - 2.73 (m, 3H), 2.68 (br t, J = 5.5 Hz, 2H), 2.28 - 2.19 (m, 2H), 1.92 - 1.56 (m, 3H), 1.47 - 1.25 (m, 3H), 1.19 - 0.91 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.40 min, m/z = 601.3 $[M+H]^+$; HPLC (Method H): Rt = 9.64 min, 99.40%.

Example 465. *N*-(3,3-Dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 465)

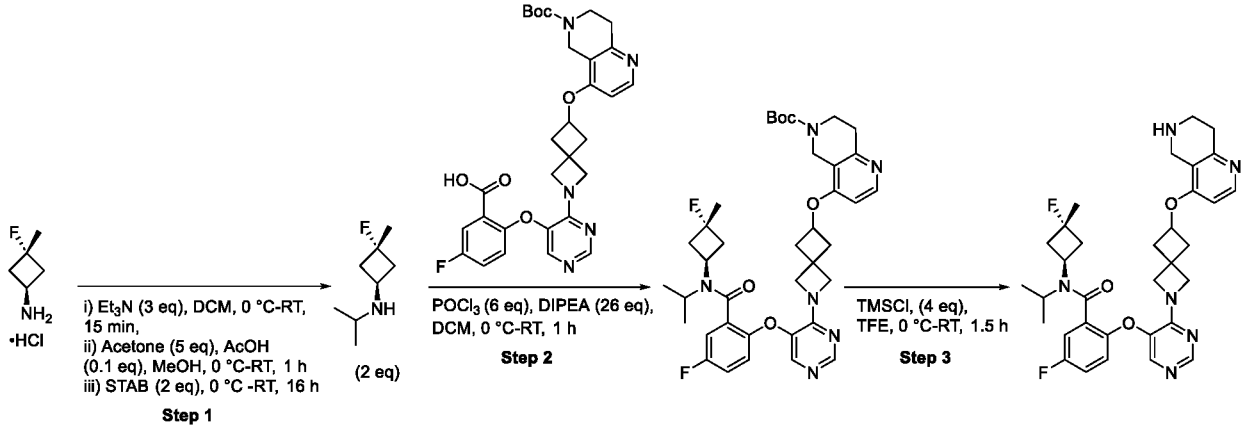


This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of *N*-(3,3-dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-

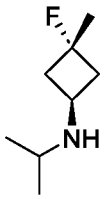
yl)pyrimidin-5-yl)oxy)benzamide, except that 5 equivalents of formaldehyde (37% in H_2O), 0.1 equivalent of AcOH and 2 equivalents of STAB were used, and MeOH was used as the solvent. After completion, the reaction was concentrated under reduced pressure. The crude was diluted with 10% MeOH in DCM and washed with aqueous sodium bicarbonate solution. The aqueous layer was re-extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford *N*-(3,3-dimethylcyclobutyl)-5-fluoro-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid.

Yield: 74.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.23 (m, 1H), 8.21 - 8.16 (m, 1H), 7.77 - 7.65 (m, 1H), 7.32 - 7.03 (m, 3H), 6.65 (br d, J = 4.8 Hz, 1H), 4.75 (quin, J = 6.6 Hz, 1H), 4.34 - 4.09 (m, 4H), 4.04 - 3.85 (m, 1H), 3.78 - 3.62 (m, 1H), 3.36 (s, 2H), 2.85 - 2.72 (m, 5H), 2.66 - 2.60 (m, 2H), 2.36 (s, 3H), 2.29 - 2.21 (m, 2H), 1.92 - 1.56 (m, 3H), 1.48 - 1.25 (m, 3H), 1.20 - 0.91 (m, 9H); LCMS (Method G): Rt = 2.07 min, m/z = 615.2 $[M+H]^+$; HPLC (Method H): Rt = 10.38 min, 99.90%.

Example 466. 5-Fluoro-*N*-((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 466)

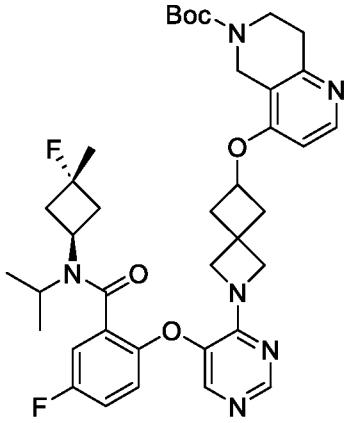


Step 1. (1r,3r)-3-Fluoro-N-isopropyl-3-methylcyclobutan-1-amine



In a dried, 50 mL two neck round bottom flask under a nitrogen atmosphere, (1*r*,3*r*)-3-fluoro-3-methylcyclobutan-1-amine hydrochloride (1 g, 7.16 mmol) was dissolved in DCM (10 mL). To this reaction mixture, TEA (3.00 mL, 21.49 mmol) was added at 0 °C, and the resulting reaction was stirred at RT for 15 min. The reaction was concentrated under reduced pressure and the residue was dissolved in MeOH (10 mL). To this reaction mixture, acetone (2.65 mL, 35.8 mmol) and AcOH (0.041 mL, 0.716 mmol) were added at 0 °C. The reaction was stirred at RT for 1 h, then was re-cooled to 0 °C. Sodium triacetoxyborohydride (3.04 g, 14.33 mmol) was added, and the reaction was stirred at RT for 16 h. The reaction was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure and the residue was diluted with saturated sodium bicarbonate solution (20 mL). The mixture was extracted with 10% MeOH in DCM (3 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to afford crude (1*r*,3*r*)-3-fluoro-*N*-isopropyl-3-methylcyclobutan-1-amine (0.6 g, 57.7% yield) as a sticky liquid. This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 - 3.42 (m, 1H), 2.79 - 2.68 (m, 1H), 2.48 - 2.36 (m, 2H), 1.98 - 1.84 (m, 2H), 1.67 - 1.37 (m, 3H), 0.97 (d, J = 6.3 Hz, 6H), one proton merged with solvent peaks.

Step 2. tert-Butyl 4-((2-(5-(4-fluoro-2-(((1r,3r)-3-fluoro-3-methylcyclobutyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate

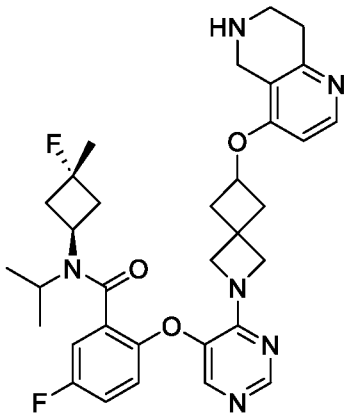


This compound was synthesized following the procedure described for the synthesis of Example 450, step 2, starting with 1 equivalent of 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-

tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic and 2 equivalents of (1*r*,3*r*)-3-fluoro-*N*-isopropyl-3-methylcyclobutan-1-amine, except that 26 equivalents of DIPEA was used. After completion, the reaction was quenched with 10% saturated sodium bicarbonate solution at 0 °C. The mixture was extracted with DCM, and the combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(5-(4-fluoro-2-(((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

Yield: 18.77%; LCMS (Method G): Rt = 2.22 min, m/z = 705.3 $[M+H]^+$, 91.61%.

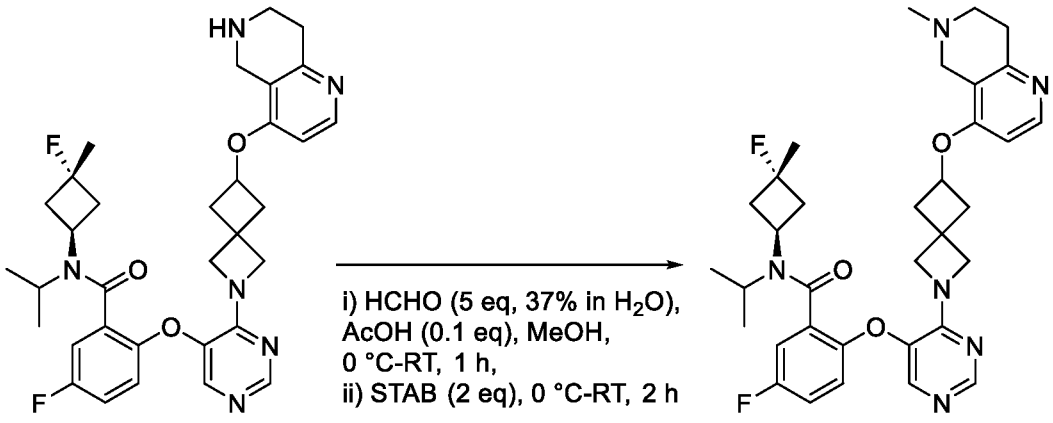
Step 3. 5-Fluoro-N-((1r,3r)-3-fluoro-3-methylcyclobutyl)-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



To a stirred solution of *tert*-butyl 4-((2-(5-(4-fluoro-2-(((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (360 mg, 0.511 mmol) in TFE (10 mL), TMSCl (0.261 mL, 2.043 mmol) was added at 0 °C. The reaction was stirred at RT for 1 h, and was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude was triturated with EtOAc (2 x 5 mL), and the organic layer was decanted. The residue was dried under vacuum, then was dissolved in DCM (2 mL). TEA (0.142 mL, 1.022 mmol) was added at RT, and the reaction was stirred at RT for 5 min, then was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were

concentrated under reduced pressure and lyophilized to obtain 5-fluoro-*N*-((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (132 mg, 41.6% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 - 8.25 (m, 1H), 8.16 (d, J = 5.7 Hz, 1H), 7.78 - 7.63 (m, 1H), 7.35 - 7.04 (m, 3H), 6.64 (d, J = 5.7 Hz, 1H), 4.72 (quin, J = 6.5 Hz, 1H), 4.37 - 4.07 (m, 5H), 3.75 - 3.62 (m, 3H), 3.22 – 3.02 (m, 1H), 2.95 (br t, J = 5.7 Hz, 2H), 2.82 - 2.74 (m, 2H), 2.71 - 2.65 (m, 2H), 2.45 - 2.36 (m, 2H), 2.39 - 2.19 (m, 3H), 1.59 - 0.94 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.79 min, m/z = 605.2 $[M+H]^+$; HPLC (Method H): Rt = 8.93 min, 97.27%; Chiral SFC (Method AAK): Rt = 3.28 min, 95.51%.

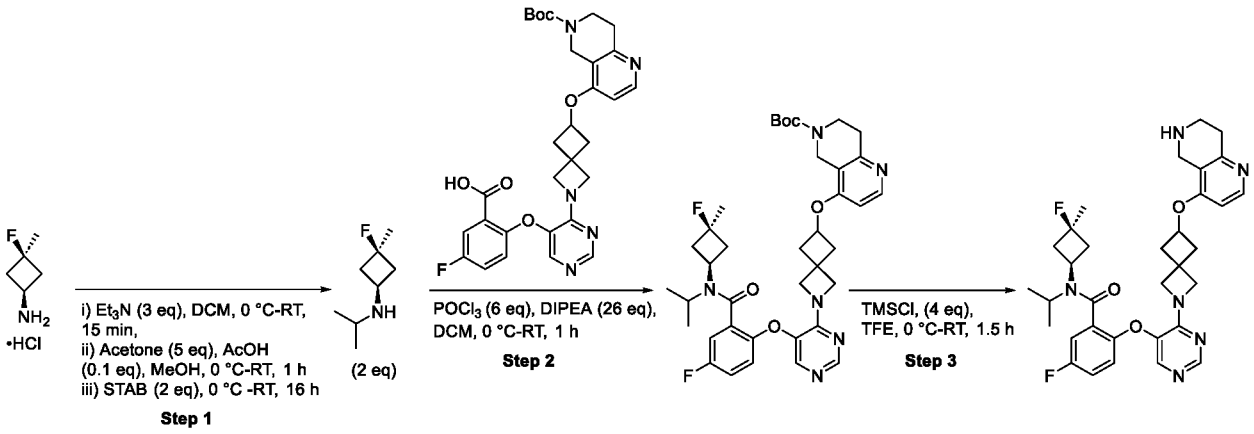
Example 467. 5-Fluoro-*N*-((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 467)



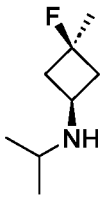
This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of 5-fluoro-*N*-((1*r*,3*r*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 5 equivalents of formaldehyde (37% in H_2O), 0.1 equivalent of AcOH, and 2 equivalents of STAB were used, and MeOH was used as the solvent. After completion, the reaction was concentrated under reduced pressure. The crude was diluted with aqueous sodium bicarbonate solution and the mixture was extracted with 10% MeOH-DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-((1*r*,3*r*)-3-

fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 68.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.24 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.78 - 7.63 (m, 1H), 7.33 - 7.04 (m, 3H), 6.65 (d, J = 5.6 Hz, 1H), 4.75 (quin, J = 6.6 Hz, 1H), 4.34 - 4.07 (m, 5H), 3.75 - 3.62 (m, 1H), 3.36 (br s, 2H), 3.25 - 2.95 (m, 2H), 2.85 - 2.74 (m, 4H), 2.65 - 2.59 (m, 2H), 2.36 (s, 3H), 2.31 - 2.17 (m, 3H), 1.57 - 0.95 (m, 9H), one proton merged with solvent peaks; LCMS (Method G): Rt = 1.91 min, m/z = 619.2 $[M+H]^+$; HPLC (Method H): Rt = 9.59 min, 97.86%; Chiral SFC (Method AAAG): Rt = 1.77 min, 100%.

Example 468. 5-Fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 468)



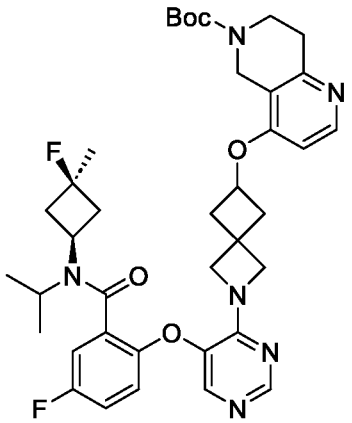
Step 1. (1s,3s)-3-Fluoro-N-isopropyl-3-methylcyclobutan-1-amine



This compound was synthesized following the procedure described for the synthesis of Example 466, step 1, starting with 1 equivalent of (1*s*,3*s*)-3-fluoro-3-methylcyclobutan-1-amine hydrochloride. After work-up, the filtrate was concentrated under reduced pressure to afford crude (1*s*,3*s*)-3-fluoro-*N*-isopropyl-3-methylcyclobutan-1-amine as a sticky solid. This material was used without further purification.

Yield: 43.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.55 - 3.43 (m, 1H), 2.80 - 2.70 (m, 1H), 2.49 - 2.37 (m, 2H), 1.99 - 1.84 (m, 2H), 1.47 - 1.38 (m, 3H), 0.97 (d, J = 6.4 Hz, 6H), one proton merged with solvent peaks.

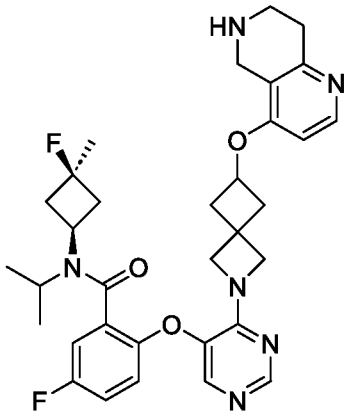
Step 2. tert-Butyl 4-((2-(5-(4-fluoro-2-(((1s,3s)-3-fluoro-3-methylcyclobutyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate



This compound was synthesized following the procedure described for the synthesis of Example 450, step 2, starting with 1 equivalent of 2-((4-(6-((6-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)-5-fluorobenzoic acid and 2 equivalents of (1*s*,3*s*)-3-fluoro-*N*-isopropyl-3-methylcyclobutan-1-amine, except that 26 equivalents of DIPEA was used. After completion, the reaction was quenched with water, and the mixture was extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude compound was purified by reverse phase column chromatography using a SiliCycle SiliaSep C18 column (120 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN) to obtain *tert*-butyl 4-((2-(5-(4-fluoro-2-(((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate as a solid.

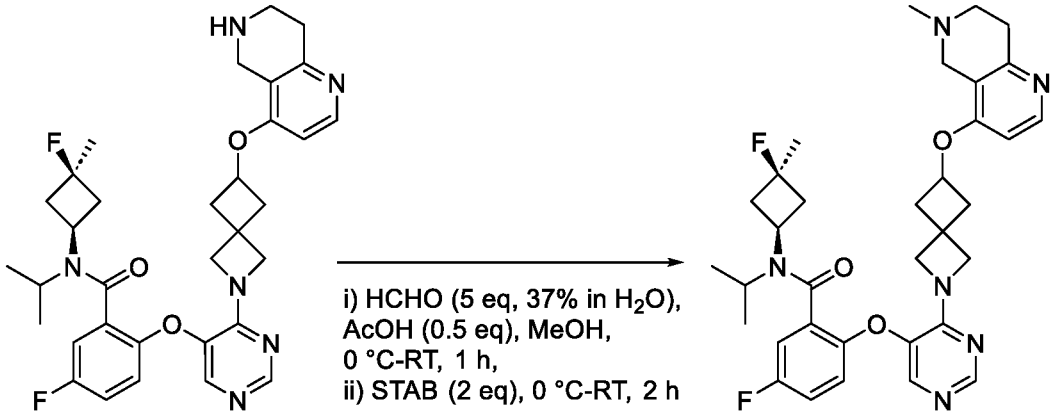
Yield: 62.3%; LCMS (Method G): Rt = 2.23 min, m/z = 705.3 $[M+H]^+$, 92.13%.

Step 3. 5-Fluoro-N-((1s,3s)-3-fluoro-3-methylcyclobutyl)-N-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide



In a 50 mL round bottom flask, *tert*-butyl 4-((2-(5-(4-fluoro-2-(((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)(isopropyl)carbamoyl)phenoxy)pyrimidin-4-yl)-2-azaspiro[3.3]heptan-6-yl)oxy)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (330 mg, 0.468 mmol) was dissolved in TFE (10 mL). TMSCl (0.239 mL, 1.873 mmol) was added to this solution at 0 °C. The reaction was stirred at RT for 1 h, and was monitored by TLC (10% MeOH in DCM). After completion, the reaction was concentrated under reduced pressure. The crude product was triturated with EtOAc (2 x 5 mL), and the organic layer was decanted. The residue was dried under vacuum, then was dissolved in DCM (2 mL). TEA (0.131 mL, 0.936 mmol) was added at 0 °C. The reaction was stirred for 5 min, then was concentrated under reduced pressure to obtain crude 5-fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (350 mg, quantitative yield). LCMS (Method G): Rt = 1.78 min, m/z = 605.2 $[M+H]^+$, 93.24%. 100 mg of 5-fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (40 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to obtain 5-fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (51.55 mg) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 - 8.22 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.79 - 7.62 (m, 1H), 7.35 - 7.03 (m, 3H), 6.63 (d, J = 5.6 Hz, 1H), 4.72 (quin, J = 6.6 Hz, 1H), 4.34 - 4.07 (m, 5H), 3.76 - 3.60 (m, 3H), 3.24 – 3.01 (m, 1H), 2.94 (br t, J = 5.8 Hz, 2H), 2.82 - 2.73 (m, 2H), 2.67 (br t, J = 5.2 Hz, 2H), 2.45 - 2.35 (m, 2H), 2.29 - 2.19 (m, 2H), 1.57 - 0.94 (m, 9H), two protons merged with solvent peaks; LCMS (Method J): Rt = 1.24 min, m/z = 605.3 $[M+H]^+$; HPLC (Method I): Rt = 7.25 min, 98.05%; Chiral SFC (Method AAK): Rt = 3.28 min, 98.27%.

Example 469. 5-Fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide (Compound No. 469)



This compound was synthesized following the procedure described for the synthesis of Example 217, starting with 1 equivalent of 5-fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide, except that 5 equivalents of formaldehyde (37% in H_2O), 0.5 equivalent of AcOH, and 2 equivalents of STAB were used, and MeOH was used as the solvent. After completion, the reaction was concentrated under reduced pressure. The crude was diluted with aqueous sodium bicarbonate solution and the mixture was extracted with 10% MeOH in DCM. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by reverse phase chromatography using a SiliCycle SiliaSep C18 column (80 g) on Biotage isolera one (Mobile phase A: 10 mM NH_4HCO_3 in water, B: ACN). The fractions were concentrated under reduced pressure and lyophilized to afford 5-fluoro-*N*-((1*s*,3*s*)-3-fluoro-3-methylcyclobutyl)-*N*-isopropyl-2-((4-(6-((6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)oxy)benzamide as a solid. Yield: 31.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 - 8.24 (m, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.80 - 7.61 (m, 1H), 7.35 - 7.03 (m, 3H), 6.65 (br d, J = 5.5 Hz, 1H), 4.75 (quin, J = 6.4 Hz, 1H), 4.34 - 4.06 (m, 5H), 3.76 - 3.62 (m, 1H), 3.36 (br s, 2H), 3.20 - 2.93 (m, 1H), 2.85 - 2.73 (m, 4H), 2.63 (br t, J = 5.7 Hz, 2H), 2.36 (s, 3H), 2.34 - 2.19 (m, 4H), 1.58 - 0.94 (m, 9H), one proton merged with solvent peaks; LCMS (Method J): Rt = 1.24 min, m/z = 619.3 $[M+H]^+$; HPLC (Method I): Rt = 7.29 min, 98.65%; Chiral SFC (Method AAAG): Rt = 1.73 min, 98.82%.

Example 470. Menin-MLL Competition and MV4;11 Cell Proliferation Assays

Menin-MLL is a competition assay between human Menin and N-terminal portion of human MLL representing amino acids 4-43 of the protein. The interaction between Menin and MLL peptide was monitored by HTRF employing Terbium labeled anti-His6 antibody directed to the N-terminal His6-tag on recombinant Menin and FITC group covalently attached to the MLL peptide. The N-terminal fragment of MLL, retained in all MLL fusion proteins, is involved in the interactions with Menin, and this protein-protein interaction is critical for the MLL fusion proteins mediated leukemogenic transformations.

For IC_{50} determination test compounds were prepared as 10 mM DMSO stock solutions. Considering DMSO as the vehicle in the assay system. Lower sub-stocks of 50µM were prepared from the 10mM stock solution. To test the compounds in assay, 3.16-fold serial dilutions are made in 100% DMSO. Mid-stock of 50x compounds (50µM) were serially diluted (3.16 fold) in 100% DMSO in Polypropylene plate. In assay plate 1 micro-litre of the previously prepared compound dilution was stamped. H-FL-Menin diluted to 4nM in assay buffer (50 mM Tris-HCl, pH 7.4, 50 mM NaCl, freshly prepared 1 mM DTT, 0.01% BSA, 0.005% Triton X-100) was pre-incubated with 8nM anti-His6-Tb for 30 min at room temperature. FITC-MLL-4-43 was diluted to 2nM in assay buffer and 25 µL was dispensed into each well of the assay plate followed by addition of 25µl of pre-incubated H-FL-Menin and anti-His6-Tb mixture. Final concentration H-FL-Menin diluted to 1nM in assay plate with 2nM anti-His6-Tb and 1nM FITC-MLL-4-43. After 1 hr incubation at room temperature, the HTRF signal was measured on the Spark multi-label plate reader. Resulting data were captured as a ratio of RFU520/RFU485 × 1000. The max values were obtained from 0% inhibition in presence of 2% DMSO and the min. values were 100% inhibition in presence of 1µM reference compound.

Example 471. Cell proliferation assay on MV4;11 and MV4-11 [M327I-heterozygous] cells using CTG assay

Test Compounds Preparation

Compounds were dissolved to obtain as 10 mM solution in DMSO. These stocks were diluted 1:5 to the top concentration to achieve 2 mM in 100% DMSO. For EC_{50} determination, compounds were serially diluted with semi-log in 100% DMSO. Each prepared DMSO solution were further diluted 1:500 in the cell culture media to obtain the 2 x dosing solutions. The Final concentrations of tested compounds in the cell culture media ranged from 0.632 nM to 2000 nM which keeps % DMSO in assay as 0.1 across the wells.

Experimental Procedure

MV4;11 [harboring the MLL-AF4; (ATCC Cat.No. CRL-9591)] & mutated cell line of MV4-11 [M327I-hetero; Source: DFCI, Boston, MA] cells were cultured in IMDM/RPMI with 10% HI FBS at 5% CO_2 and 37 °C. The cell suspension containing 150,000 cells/mL in the culture medium was dispensed in 96-well cell culture plates 100 µL (15,000 cell/well) per well. Then 100 µL of 2 x dosing media with test compounds were added to each well. Cells were cultured for 72 h at 37 °C and 5% CO_2 in a humidified incubator.

Post 72 h incubation, cultured cells were resuspended and 100 µL of the suspension from the assay plate was transferred into 96-well black OptiPlate (PerkinElmer Cat. No. 6005320). To this, 100 µL of Cell Titer Glo reagent was added, assay plates were shaken for 5 min at RT, and luminescence was read on Tecan Spark (Tecan) plate reader.

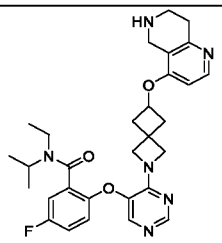
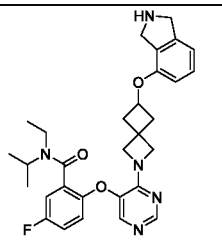
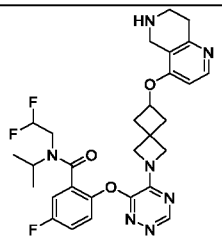
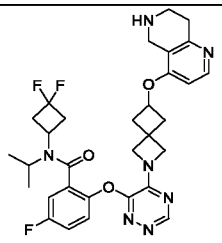
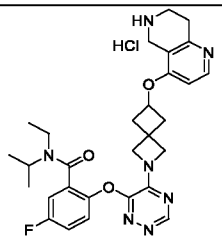
Data Analysis

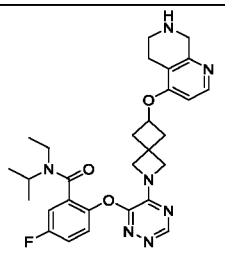
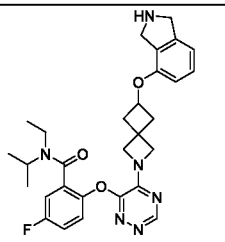
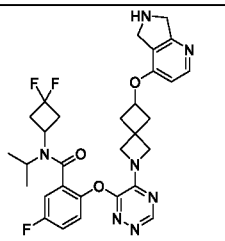
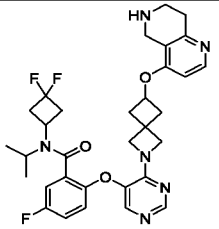
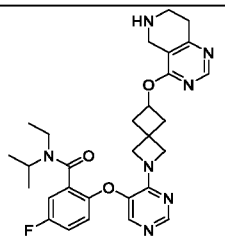
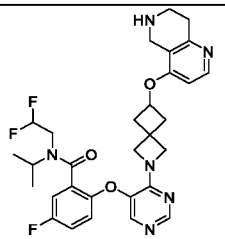
Percent inhibition values were calculated based on the high luminescence signal obtained with 0.1% DMSO control and the low signal observed with 5 µM Revumenib. The percent inhibition vs. concentration data were fit into a four-parameter model, and EC_{50} values were calculated from the fit as the concentrations corresponding to the inflection points on the dose-response curves. Data is shown in Table 2.

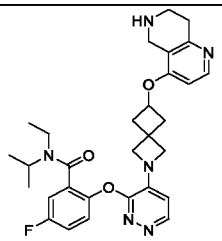
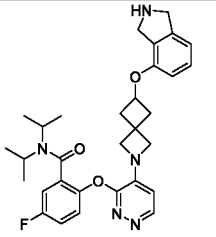
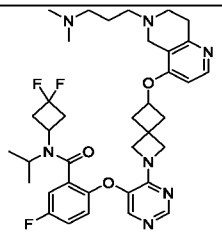
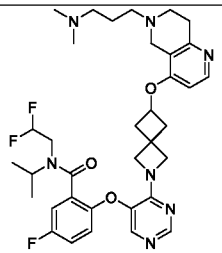
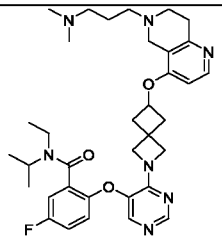
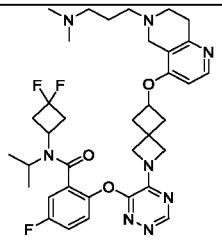
Example 472. Determination of Binding Constants to Menin-MLL

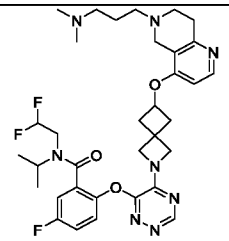
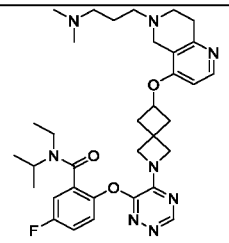
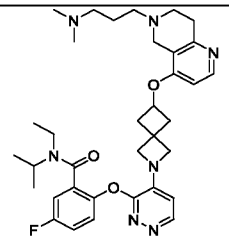
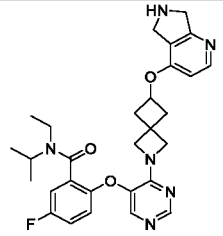
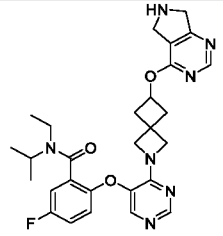
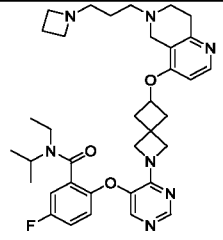
For Ki determination, individual compounds were prepared as 10 mM DMSO stock solutions. Considering DMSO as the vehicle in the assay system. Lower sub-stocks of 16µM were prepared from the 10mM stock solution. To test the compounds in assay, 3.16-fold serial dilutions are made in 100% DMSO. Mid-stock of 50x compounds (16µM) were serially diluted (3.16 fold) in 100% DMSO in Polypropylene plate. In assay plate 1 micro-litre of the previously prepared compound dilution was stamped. H-FL-Menin diluted to 1nM in assay buffer (50 mM Tris-HCl, pH 7.4, 50 mM NaCl, freshly prepared 1 mM DTT, 0.01% BSA, 0.005% Triton X-100) and pre-incubated with 2nM anti-His6-Tb for 30 min at room temperature and then 25µl was dispensed into each well. FITC-MLL-4-43 was diluted to 6.4nM in assay buffer and 25 µL was dispensed into each well of the assay plate followed by addition of 25µl of pre-incubated H-FL-Menin and anti-His6-Tb mixture. Final concentration H-FL-Menin diluted to 0.25nM in assay plate with 0.5nM anti-His6-Tb and 3.2nM FITC-MLL-4-43. After 24 hr incubation at room temperature, the HTRF signal was measured on the Spark multi-label plate reader. Resulting data were captured as a ratio of RFU520/RFU485 × 1000. The max values were obtained from 0% inhibition in presence of 2% DMSO and the min. values were 100% inhibition in presence of 320nM reference compound. Data is shown in Table 2.

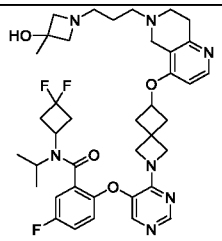
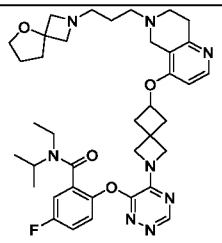
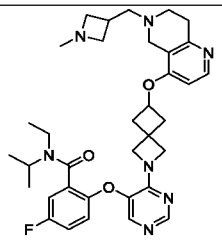
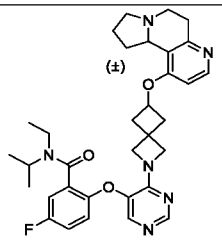
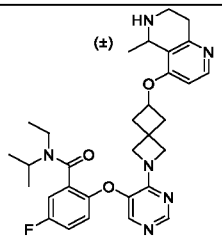
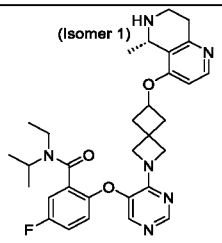
Table 2. Shows (i) Menin-MLL binding data according to Homogeneous Time Resolved Fluorescence (HTRF) assay with (i) individual compound Ki (nM) and (ii) the EC_{50} (nM) against MV4;11 and MV4;11 M327I leukemia cell lines. Ki data (nM) are provided below ("n/a" refers to data not available; "+++" means <1.0 nM; "++" means ≥1.0 nM and <1.5 nM; and "+" means ≥1.5 nM). EC_{50} (nM) against MV4;11 and MV4;11 M327I data are provided below ("n/a" refers to data not available; "+++" means <100 nM; "++" means ≥100 nM and <1000 nM; and "+" means ≥1000 nM).

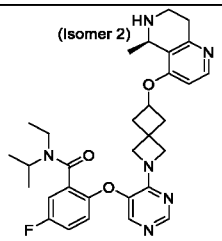
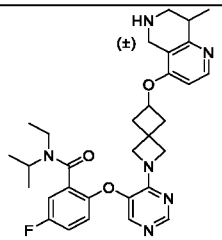
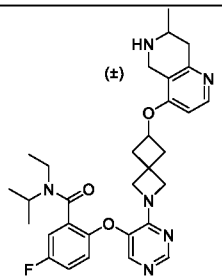
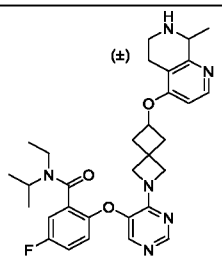
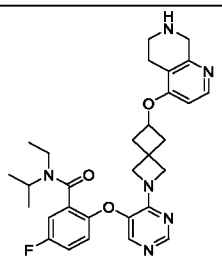
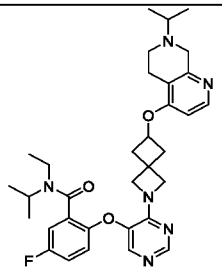
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
23		+++	+++	+++
1		+++	+++	+++
82		+++	+++	+++
172		+++	+++	+++
90		+++	+++	+++

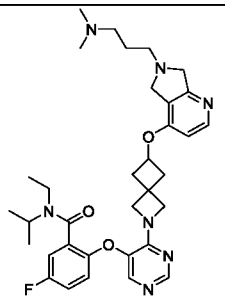
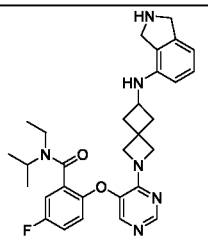
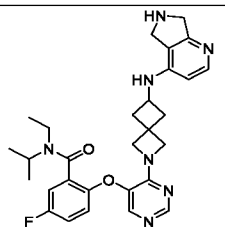
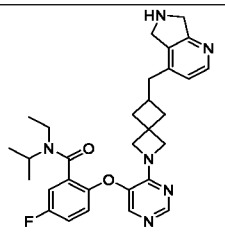
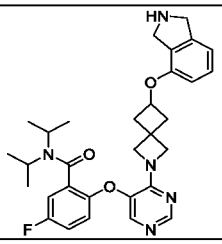
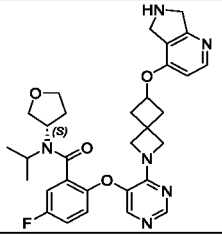
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
155		+++	+++	+++
7		+++	+++	n/a
283		+++	+++	+++
131		+++	+++	+++
68		+++	+++	++
58		+++	+++	+++

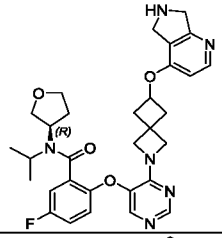
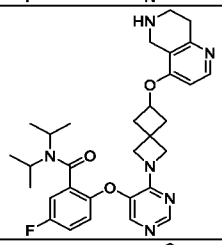
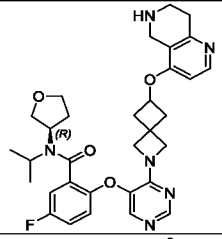
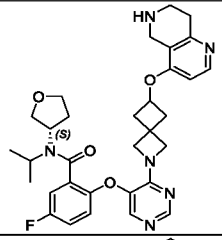
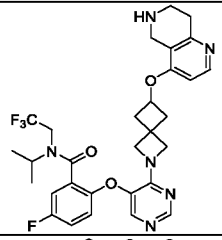
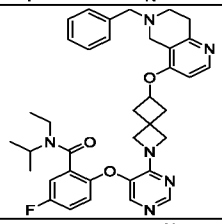
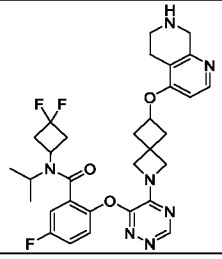
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
213		+++	+++	+++
19		+++	+++	n/a
176		+++	+++	+++
85		+++	+++	+++
65		+++	+++	+++
187		+++	+++	+++

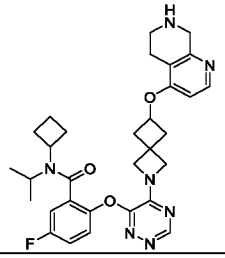
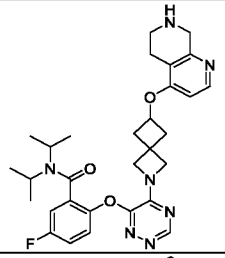
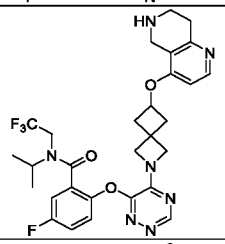
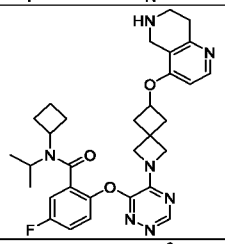
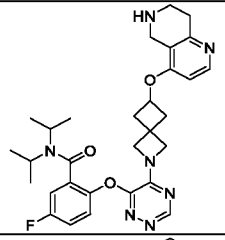
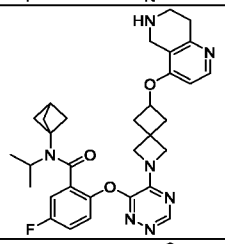
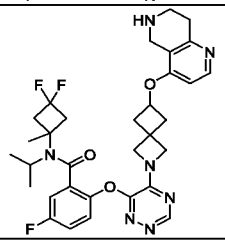
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
88		+++	+++	+++
89		+++	+++	+++
229		+++	+++	+++
4		+++	+++	+++
2		+++	++	n/a
92		+++	+++	+++

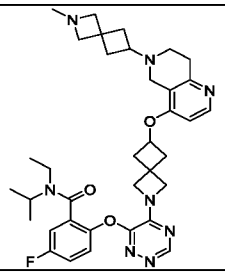
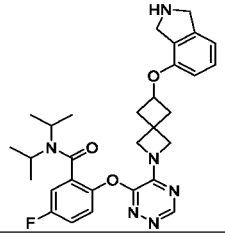
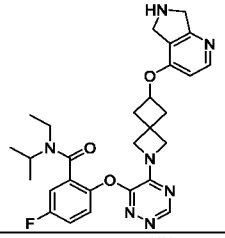
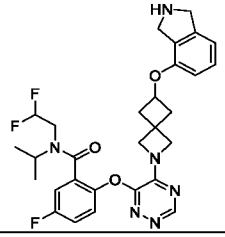
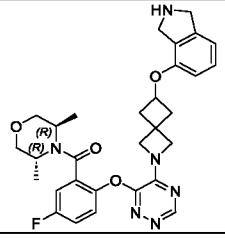
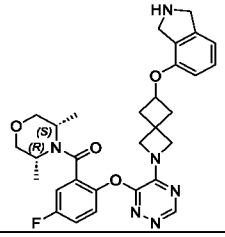
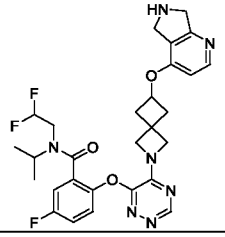
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
214		+++	+++	+++
299		+++	+++	+++
75		+++	+++	+++
241		+++	+++	+++
132		+++	+++	+++
149		+++	+++	+++

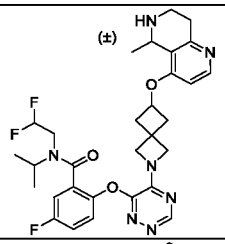
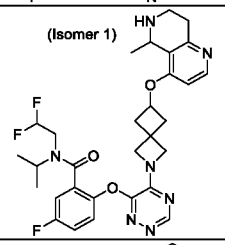
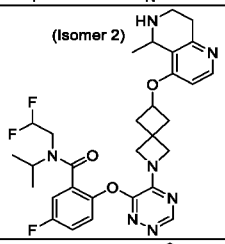
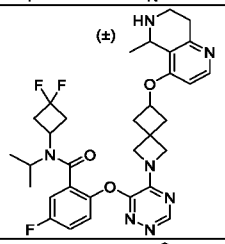
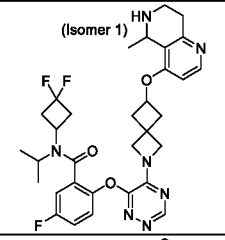
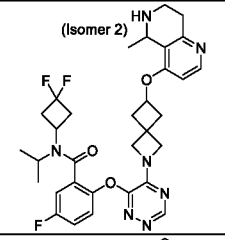
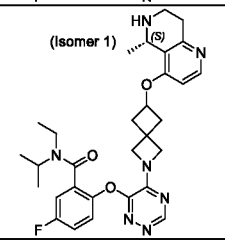
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
150		+++	+++	+++
189		+++	+++	+++
180		+++	+++	+++
209		+++	+++	+++
91		+++	+++	+++
208		+++	+++	+++

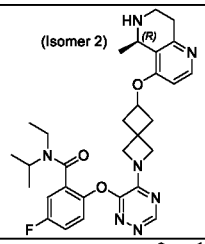
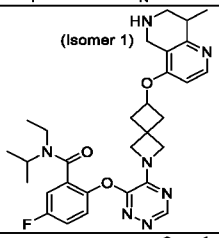
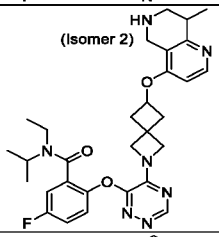
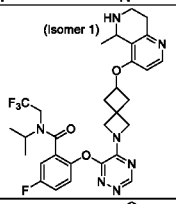
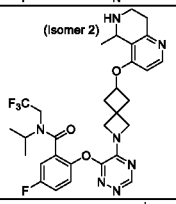
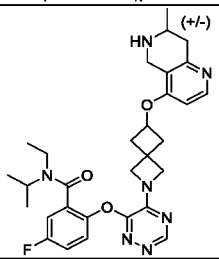
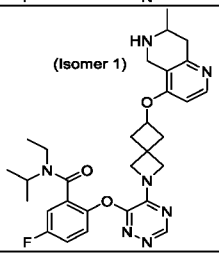
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
45		+++	+++	+++
20		+++	+++	n/a
13		+++	++	n/a
17		+++	+++	+++
3		+++	+++	n/a
44		+++	+++	+++

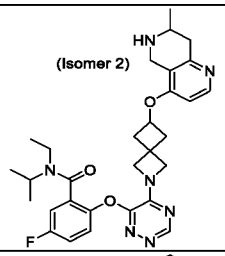
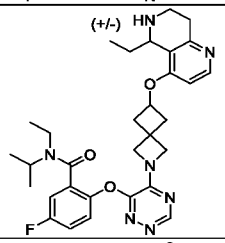
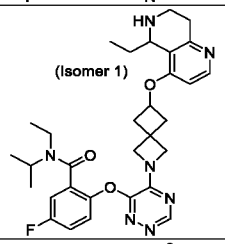
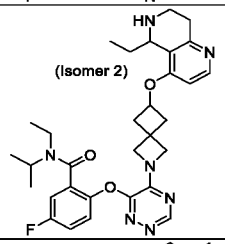
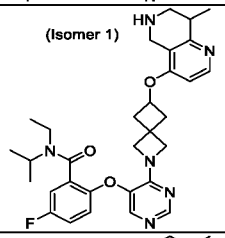
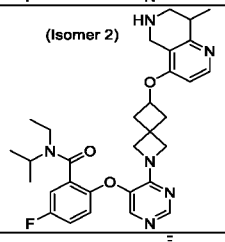
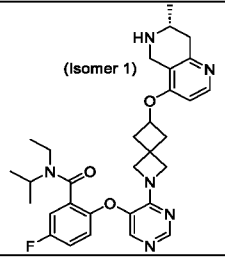
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
50		+++	+++	+++
52		+++	+++	+++
54		+++	+++	+++
57		+++	+++	+++
67		+++	+++	+++
253		+++	+++	+++
201		+++	+++	+++

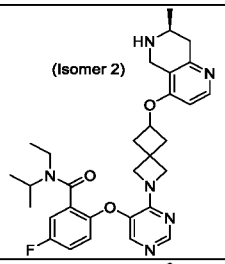
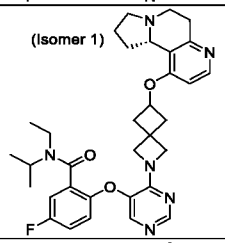
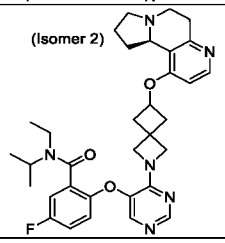
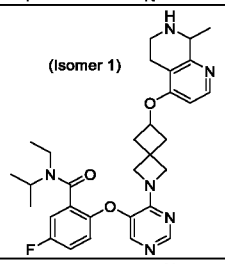
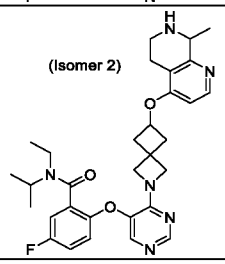
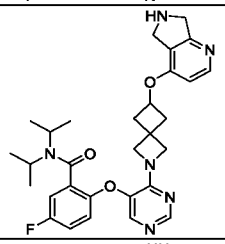
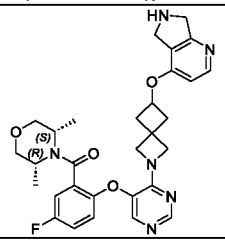
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
183		+	+++	+++
151		+++	+++	+++
235		+++	+++	+++
179		+++	+++	+++
105		+++	+++	+++
310		+++	+++	+++
261		+++	+++	+++

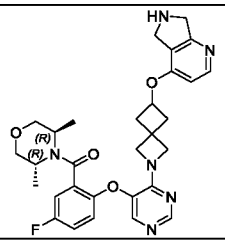
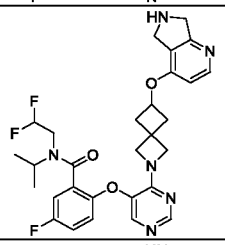
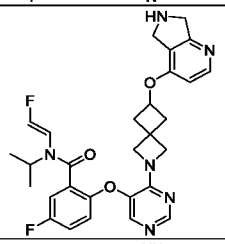
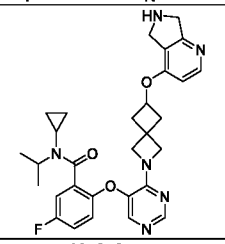
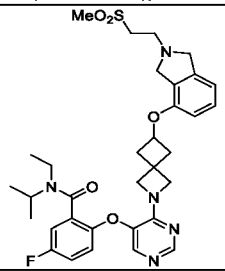
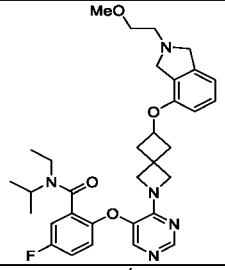
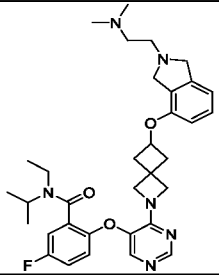
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
284		+++	+++	+++
6		+++	+++	n/a
285		+++	+++	+++
11		+++	+++	n/a
10		+++	+++	n/a
39		+++	+++	n/a
311		+++	+++	+++

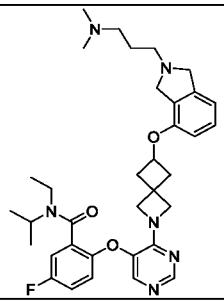
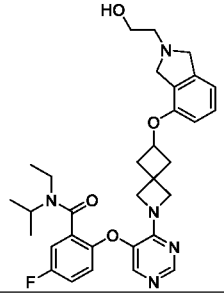
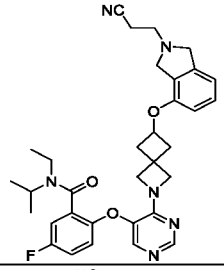
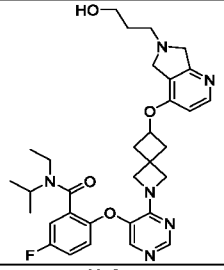
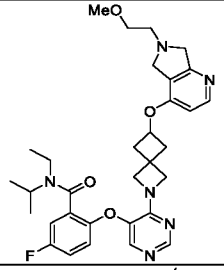
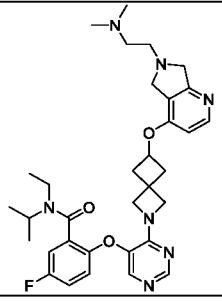
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
202		+++	+++	+++
210		+++	++	++
211		+++	+++	+++
238		+++	+++	+++
263		+++	+++	++
264		+++	+++	+++
190		+++	+++	++

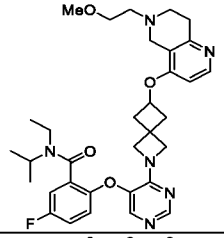
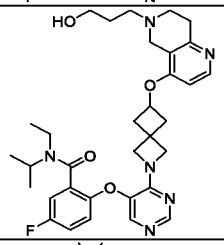
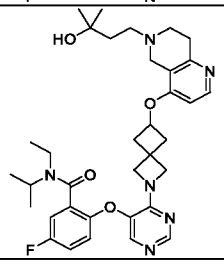
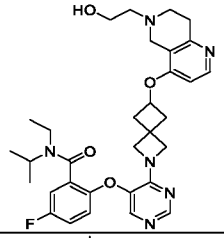
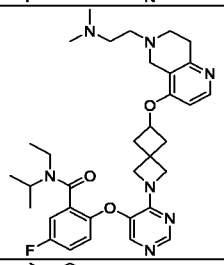
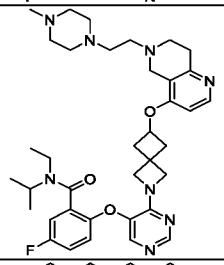
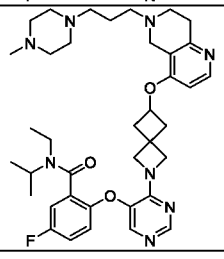
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
191		+++	+++	+++
290		+++	+++	+++
291		+++	+++	+++
320		+++	+++	++
321		+++	+++	+++
258		+++	+++	+++
286		+++	+++	+++

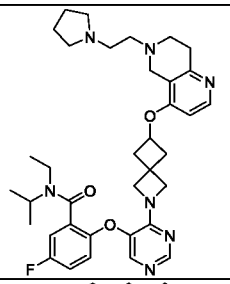
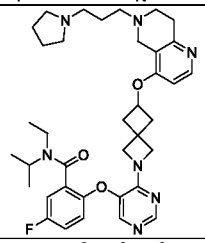
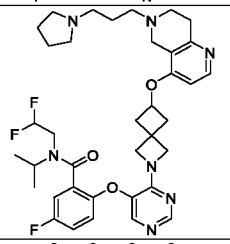
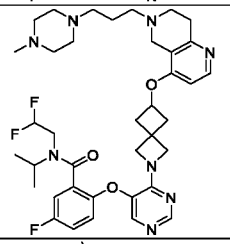
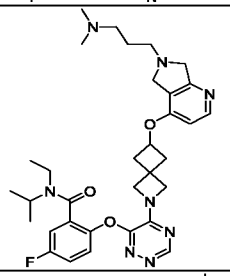
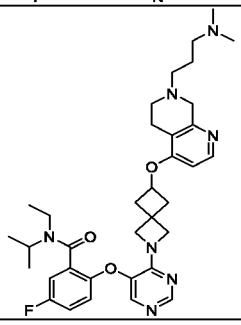
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
287		+++	+++	+++
219		+++	+++	+++
230		+++	+++	+++
231		+++	+++	+++
203		+++	+++	+++
204		+++	+++	+++
193		+++	+++	+++

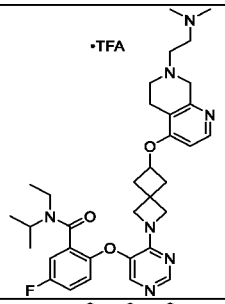
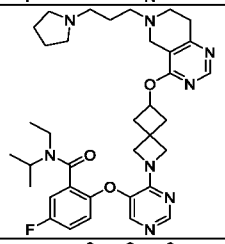
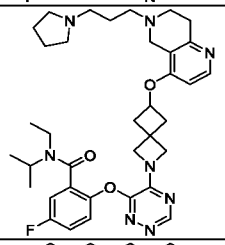
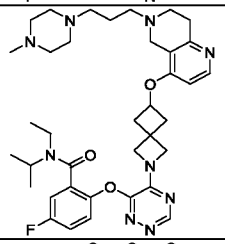
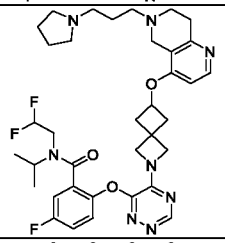
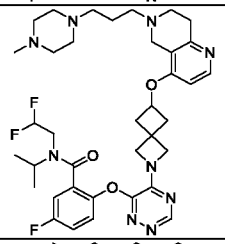
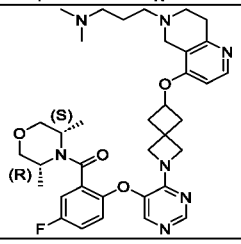
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
194		+++	+++	+++
249		+++	+++	++
250		+++	+++	+++
224		+++	+++	+++
225		+++	+++	+++
16		+++	+++	+++
21		+++	+++	n/a

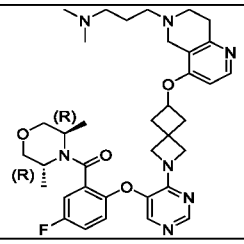
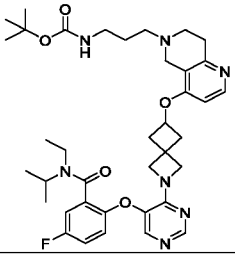
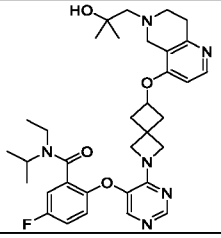
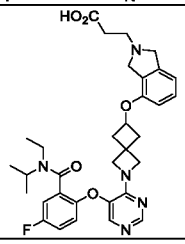
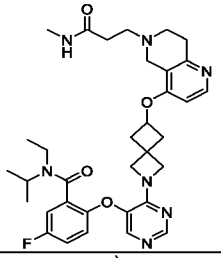
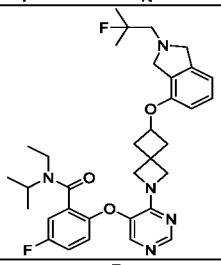
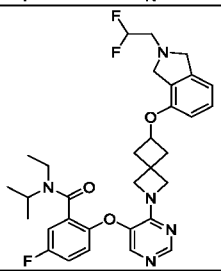
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
24		+++	+++	+++
15		+++	+++	n/a
18		+++	+++	n/a
48		+++	+++	+++
29		+++	+++	n/a
36		+++	+++	+++
37		+++	+++	+++

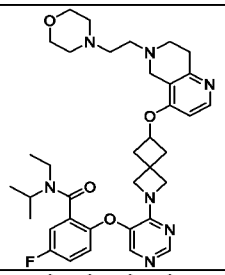
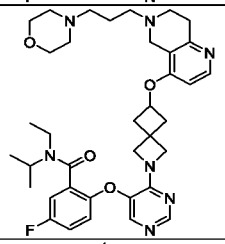
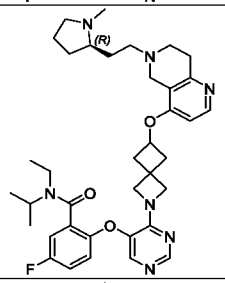
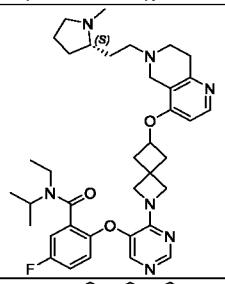
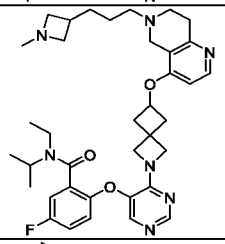
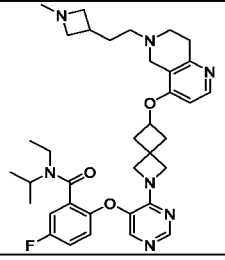
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
38		+++	+++	+++
42		+++	+++	+++
34		+++	++	n/a
51		+++	+++	+++
43		+++	+++	+++
46		+++	+++	n/a

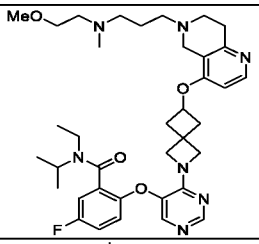
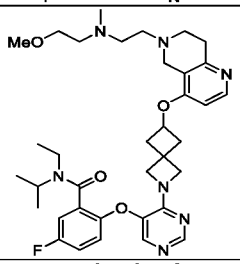
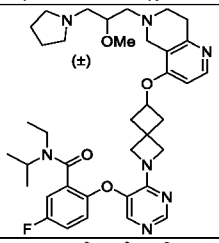
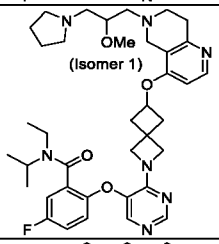
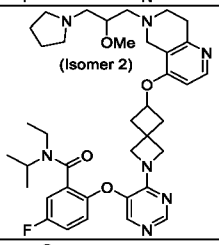
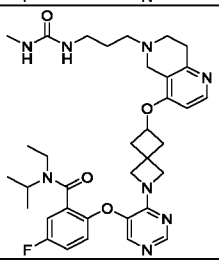
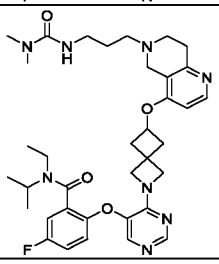
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
60		+++	+++	+++
62		+++	+++	+++
63		+++	+++	+++
66		+++	+++	+++
69		+++	+++	+++
70		+++	+++	+++
71		+++	+++	+++

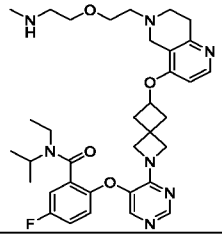
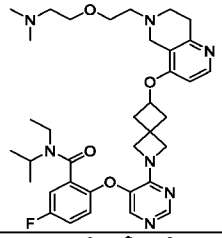
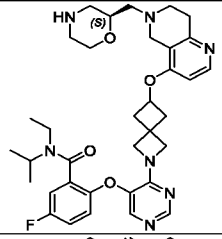
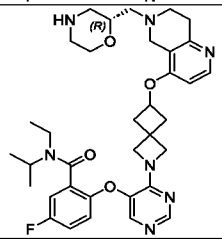
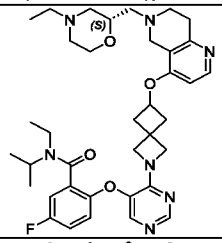
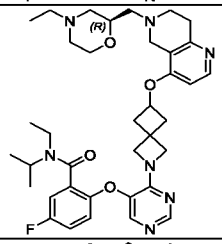
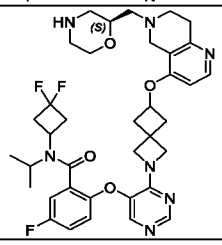
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
79		+++	+++	+++
81		+++	+++	+++
97		+++	+++	+++
98		+++	+++	+++
296		+++	+++	+++
116		+++	+++	+++

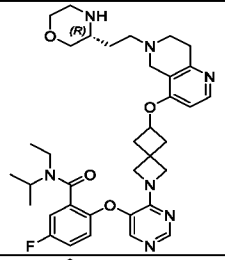
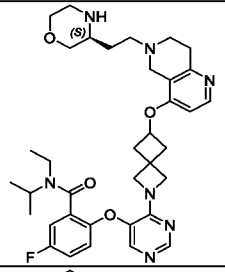
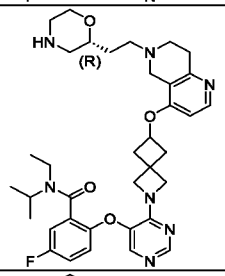
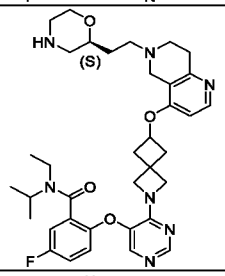
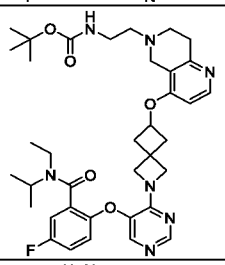
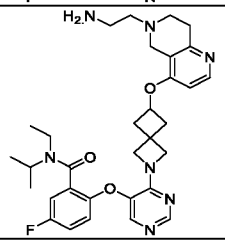
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
125-a		++	++	++
94		+++	+++	++
112		+++	+++	+++
113		+++	+++	+++
147		+++	+++	+++
152		+++	+++	+++
83		+++	+++	+++

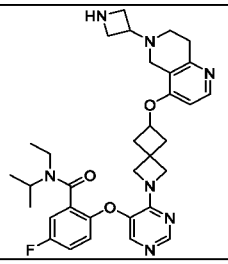
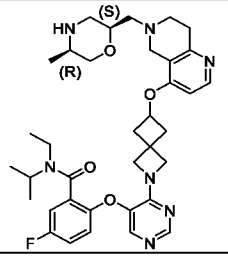
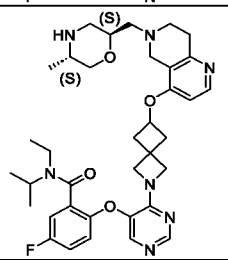
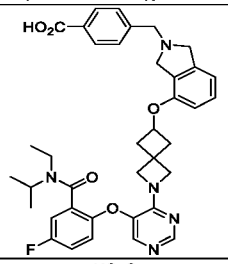
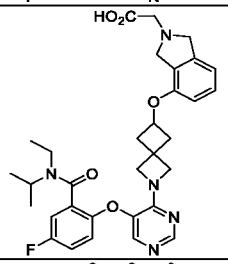
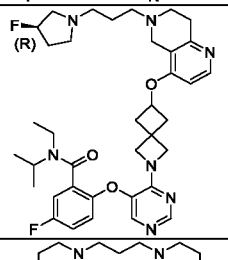
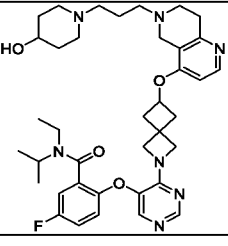
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
77		+++	+++	+++
119		+++	+++	+++
64		+++	+++	+++
33		+++	++	n/a
115		+++	+++	+++
41		+++	+++	n/a
49		+++	++	n/a

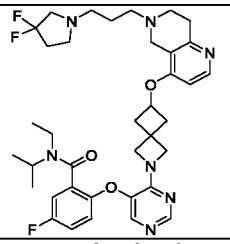
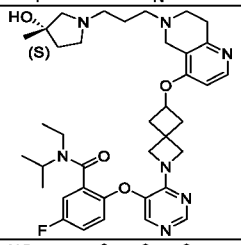
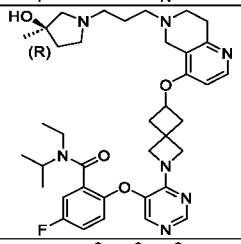
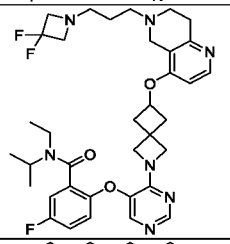
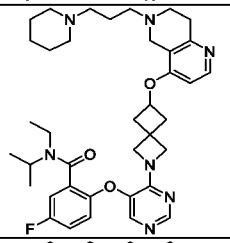
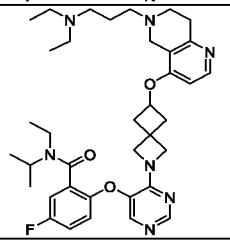
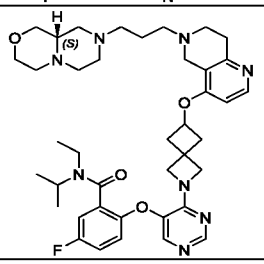
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
73		+++	+++	+++
72		+++	+++	+++
103		+++	+++	+++
102		+++	+++	+++
269		+++	+++	+++
273		+++	+++	+++

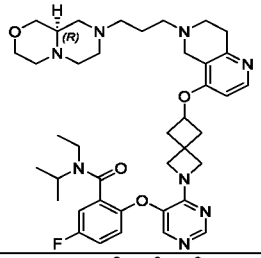
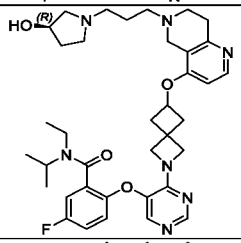
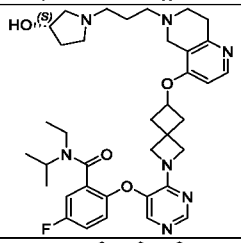
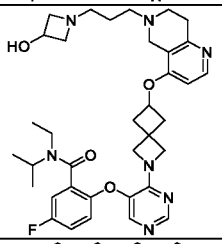
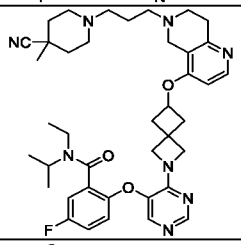
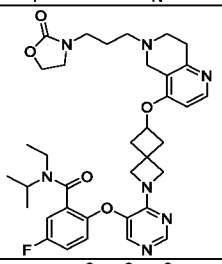
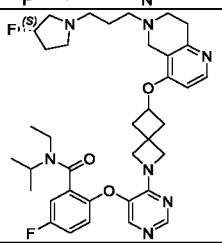
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
74		+++	+++	+++
84		+++	+++	+++
207		+++	+++	+++
259		+++	+++	+++
260		+++	+++	+++
143		+++	+++	+++
148		+++	+++	+++

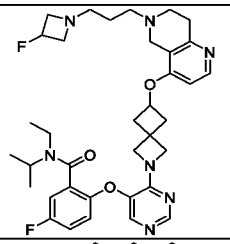
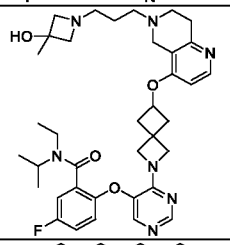
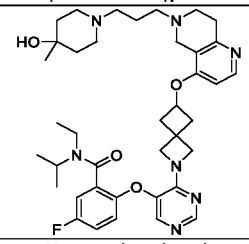
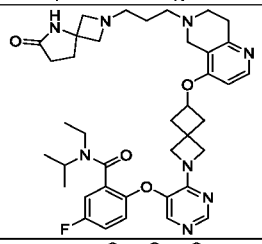
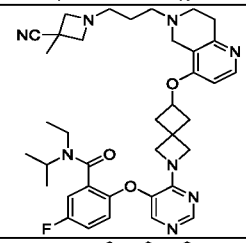
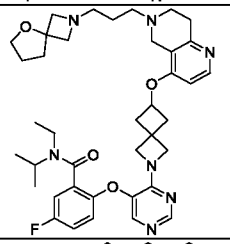
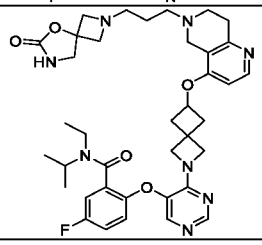
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
216		+++	+++	++
232		+++	+++	+++
217		+++	+++	+++
218		+++	+++	+++
254		+++	+++	+++
255		+++	+++	+++
246		+++	+++	+++

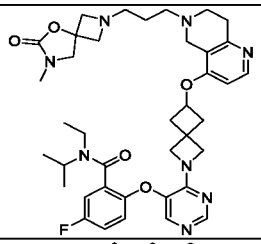
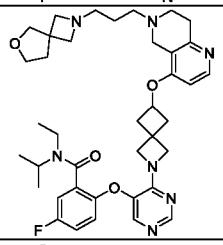
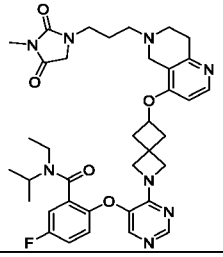
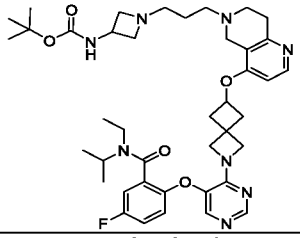
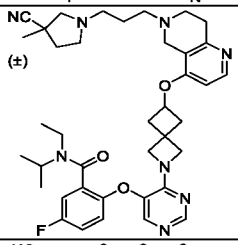
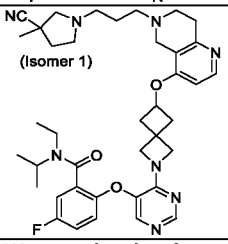
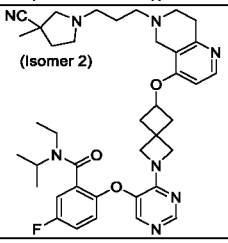
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
268		+++	+++	+++
275		+++	+++	+++
276		+++	+++	+++
277		+++	+++	+++
142		+++	+++	+++
159		+++	+++	+++

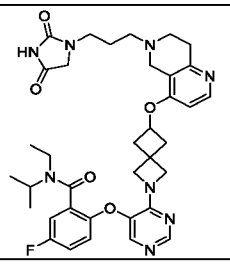
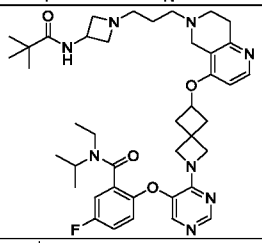
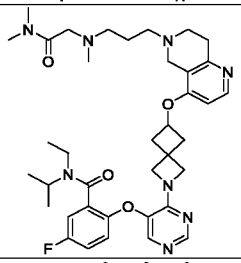
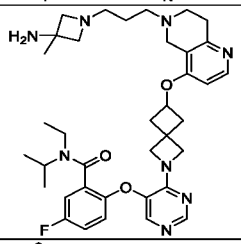
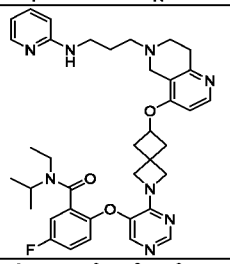
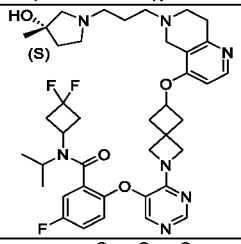
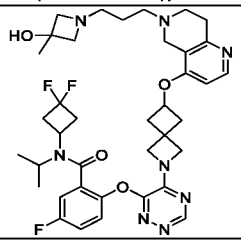
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
101		+++	+++	++
267		+++	+++	+++
272		+++	+++	+++
31		+++	+++	n/a
32		+++	++	n/a
156		+++	+++	+++
123		+++	+++	+++

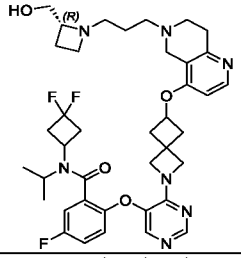
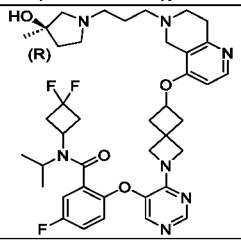
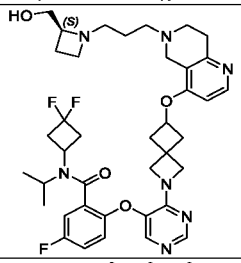
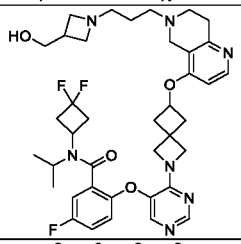
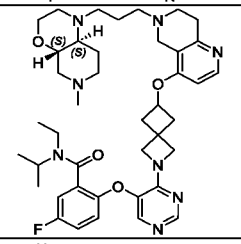
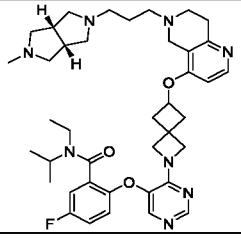
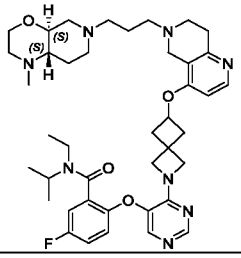
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
175		+++	+++	+++
157		+++	+++	+++
158		+++	+++	+++
170		+++	+++	+++
99		+++	+++	+++
100		+++	+++	+++
109		+++	+++	+++

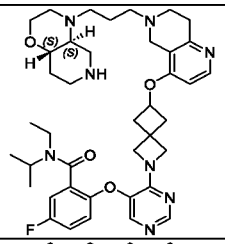
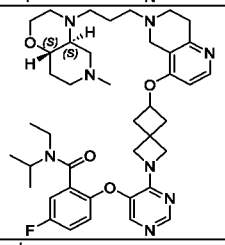
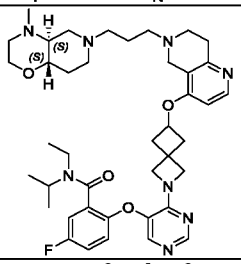
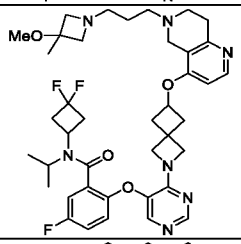
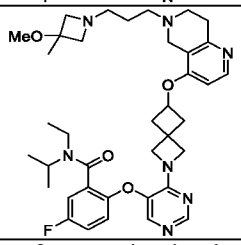
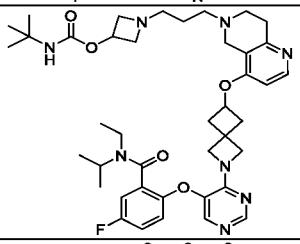
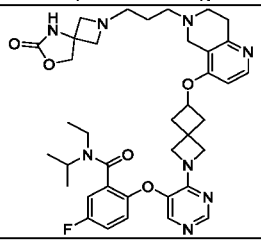
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
108		+++	+++	+++
117		+++	+++	+++
126		+++	+++	+++
121		+++	+++	+++
129		+++	+++	+++
145		+++	+++	+++
146		+++	+++	+++

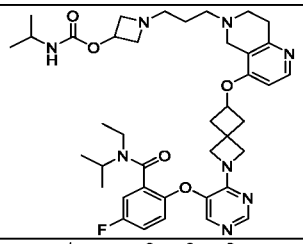
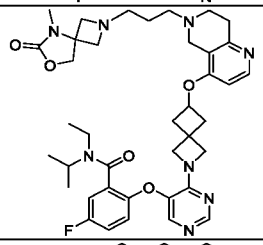
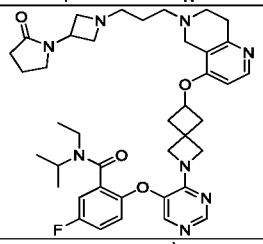
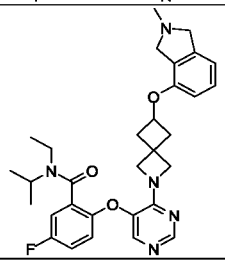
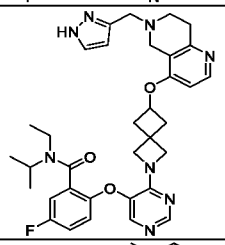
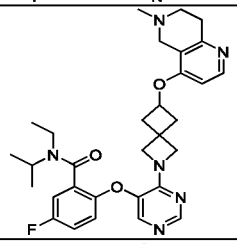
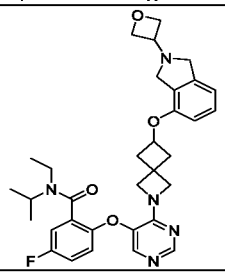
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
163		+++	+++	+++
168		+++	+++	+++
134		+++	+++	+++
141		+++	+++	+++
174		+++	+++	+++
295		+++	+++	+++
237		+++	+++	+++

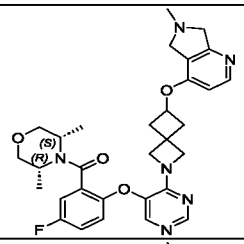
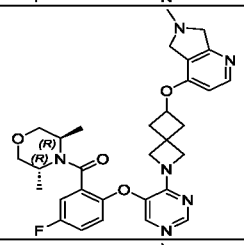
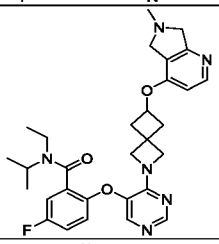
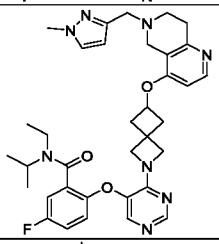
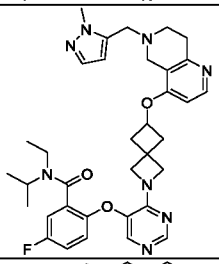
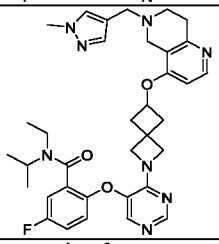
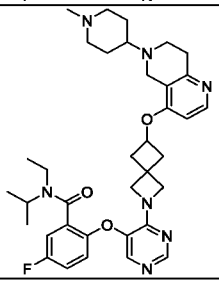
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
242		+++	+++	+++
270		+++	+++	+++
292		+++	+++	+++
153		+++	+++	+++
181		+++	+++	+++
198		+++	+++	+++
199		+++	+++	+++

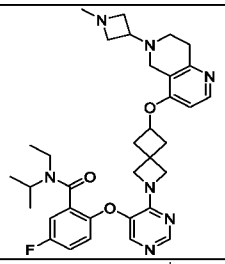
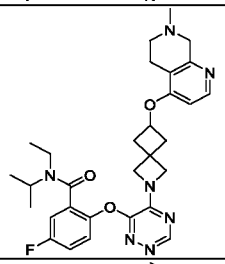
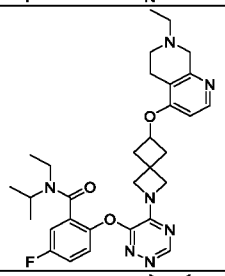
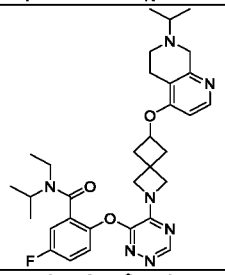
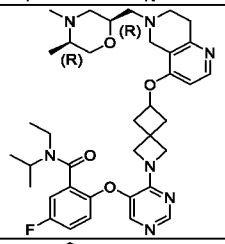
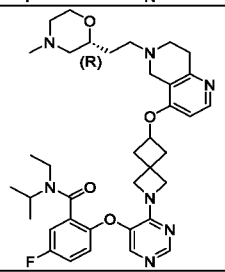
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
245		+++	+++	+++
206		+++	+++	+++
248		+++	+++	+++
196		+++	+++	++
169		+++	+++	+++
244		+++	+++	+++
205		+++	+++	+++

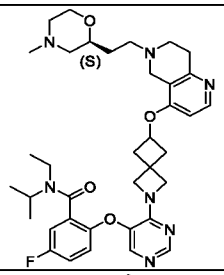
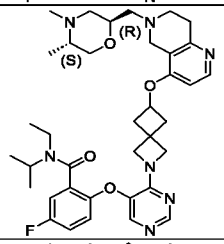
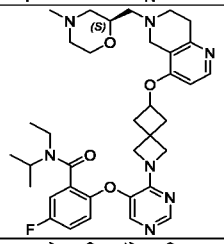
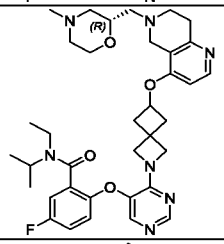
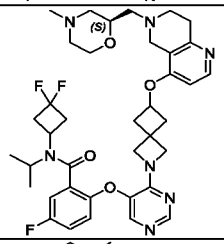
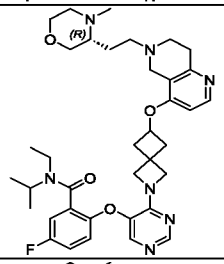
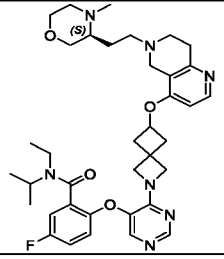
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
239		+++	+++	+++
252		+++	+++	+++
279		+++	+++	+++
240		+++	+++	+++
136		+++	+++	+++
110		+++	+++	+++
111		+++	+++	+++

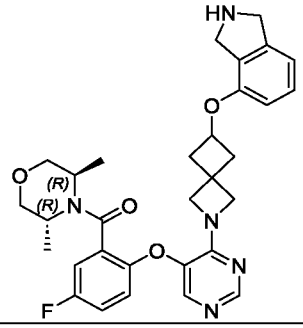
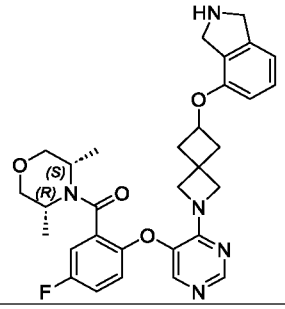
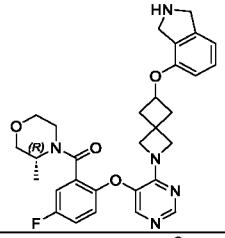
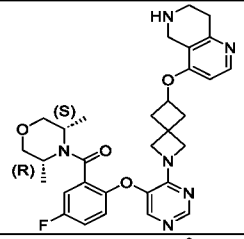
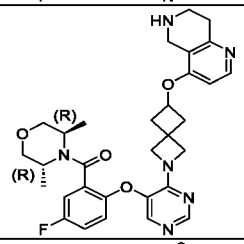
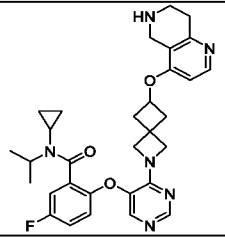
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
107		+++	+++	+++
130		+++	+++	+++
106		+++	+++	+++
262		+++	+++	+++
293		+++	+++	+++
220		+++	+++	+++
236		+++	+++	+++

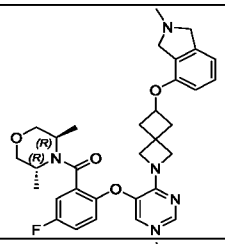
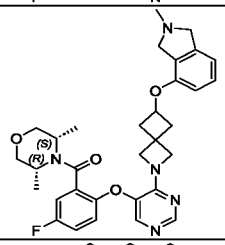
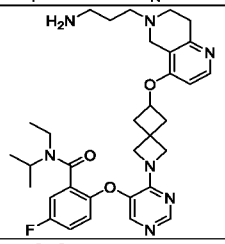
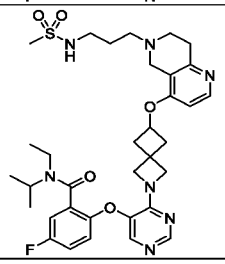
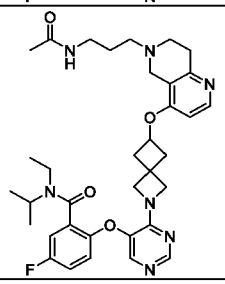
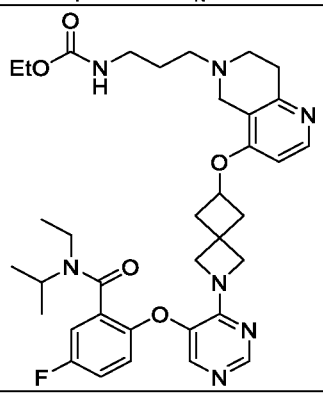
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
256		+++	+++	+++
257		+++	+++	+++
221		+++	+++	+++
22		+++	+++	n/a
87		+++	+++	+++
59		+++	+++	+++
28		+++	+++	n/a

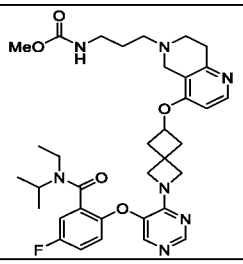
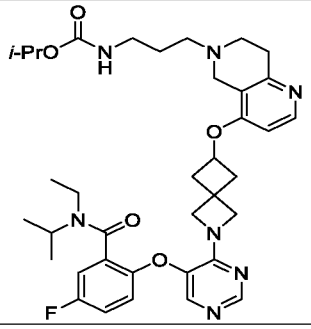
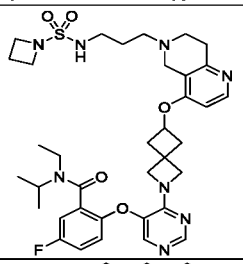
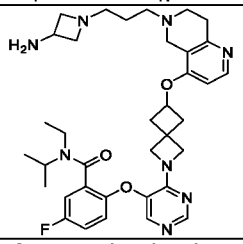
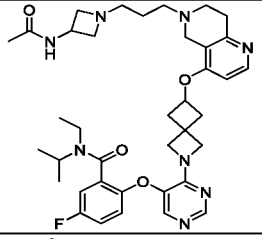
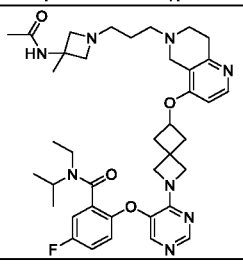
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
35		+++	+++	n/a
30		+++	+++	+++
27		+++	+++	+++
93		+++	+++	+++
96		+++	+++	+++
95		+++	+++	+++
76		+++	+++	+++

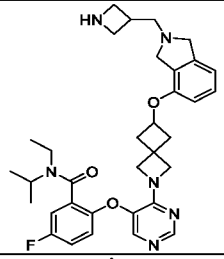
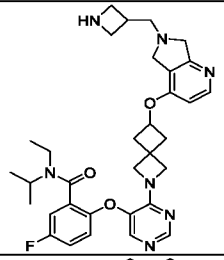
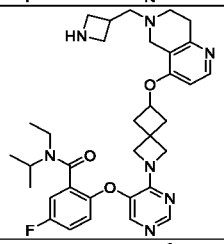
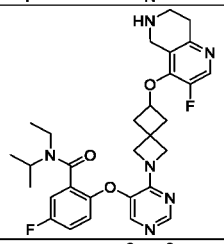
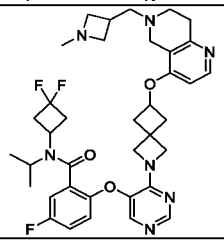
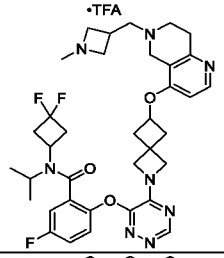
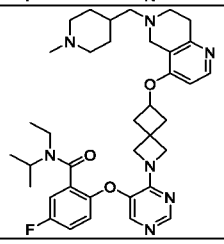
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
133		+++	++	++
195		+++	+++	+++
200		+++	+++	+++
227		+++	+++	+++
294		+++	+++	+++
297		+++	+++	+++

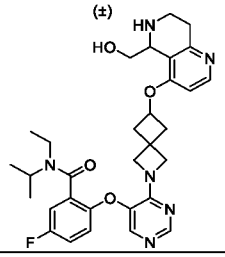
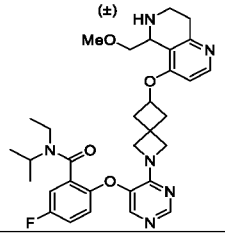
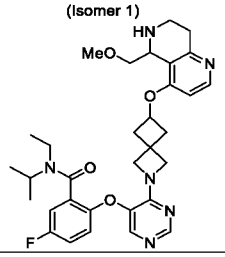
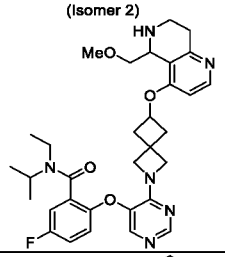
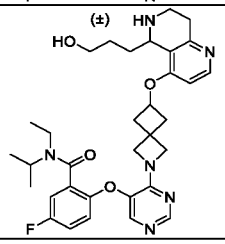
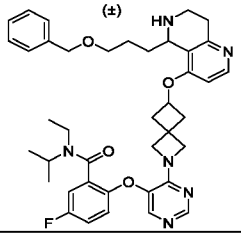
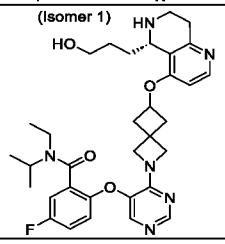
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
298		+++	+++	+++
302		+++	+++	+++
222		+++	+++	+++
223		+++	+++	+++
247		+++	+++	+++
274		+++	+++	+++
303		+++	+++	+++

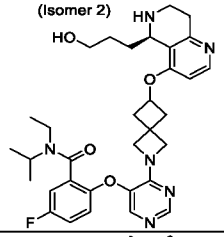
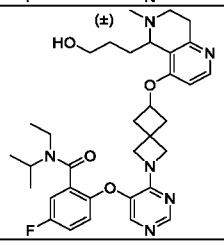
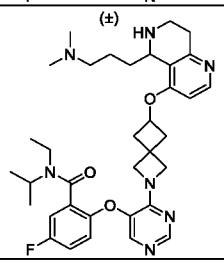
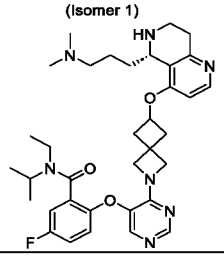
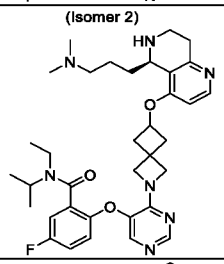
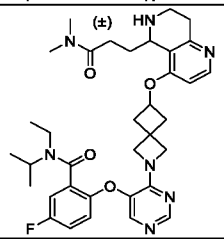
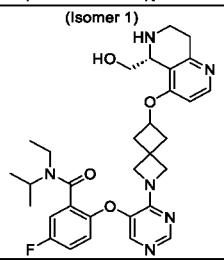
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
5		+++	+++	n/a
8		+++	+++	n/a
9		+++	+++	n/a
55		+++	+++	+++
56		+++	+++	+++
53		+++	+++	+++

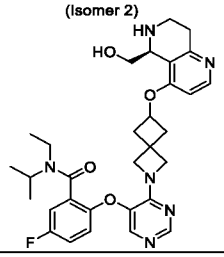
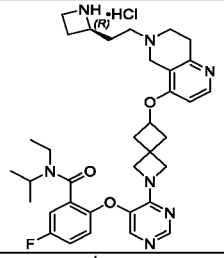
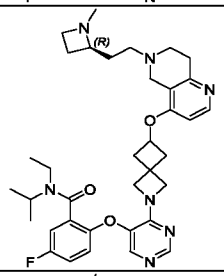
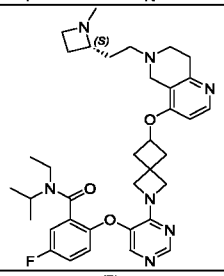
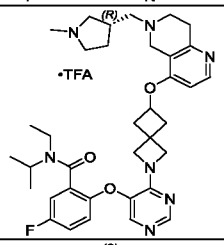
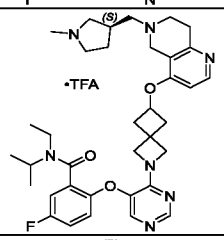
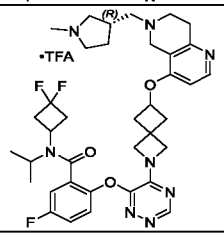
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
25		+++	+++	n/a
26		+++	+++	n/a
128		+++	+++	+++
127		+++	+++	+++
120		+++	+++	+++
137		+++	+++	+++

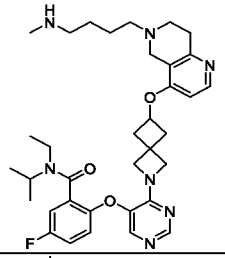
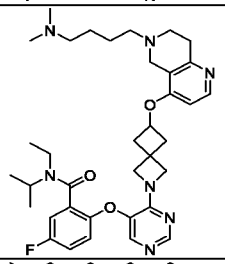
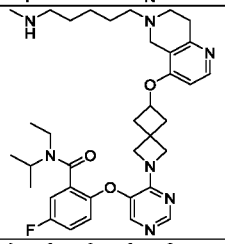
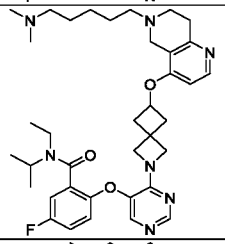
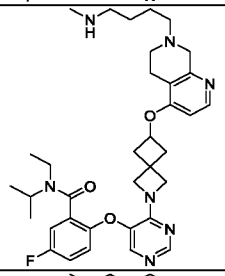
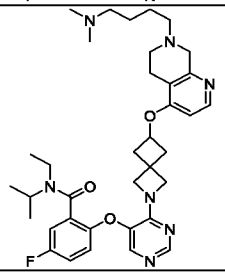
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
138		+++	+++	+++
139		+++	+++	+++
162		+++	+++	+++
154		+++	+++	++
164		+++	+++	++
188		+++	+++	++

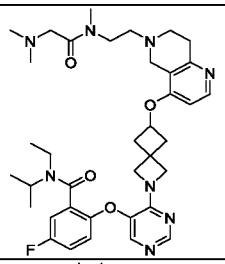
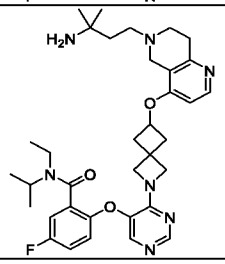
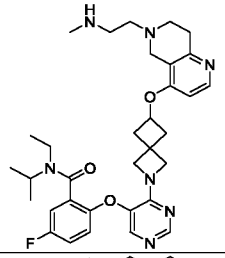
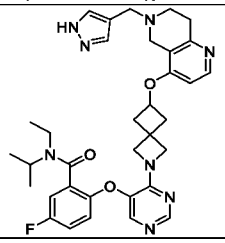
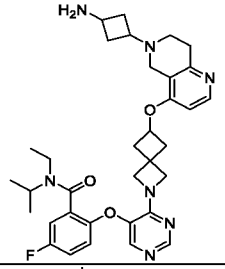
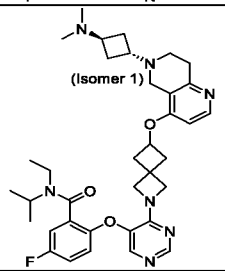
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
40		+++	+++	+++
47		+++	+++	n/a
61		+++	+++	++
192		+++	+++	+++
266		+++	+++	+++
271-a		+++	+++	+++
80		+++	+++	+++

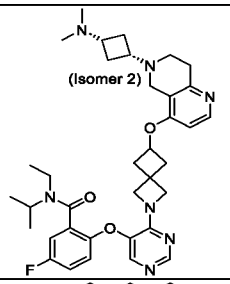
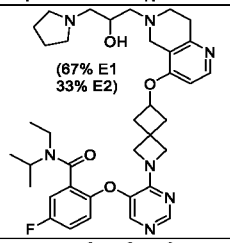
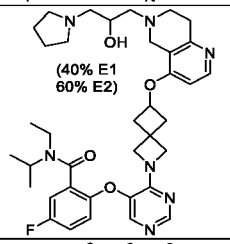
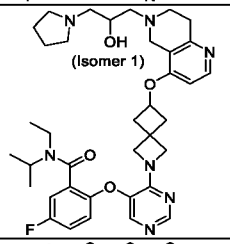
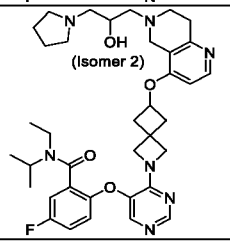
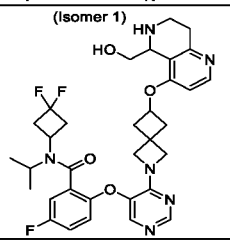
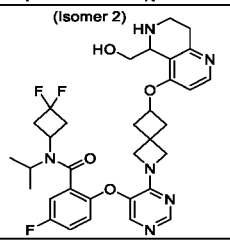
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
251		+++	+++	+++
280		+++	+++	+++
288		+++	+++	++
289		+++	+++	+++
212		+++	+++	+++
215		+++	+++	+++
233		+++	+++	++

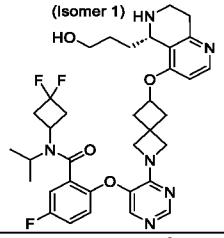
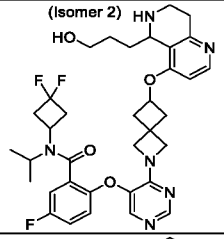
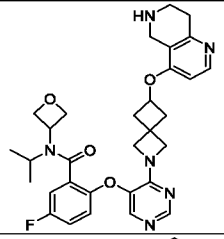
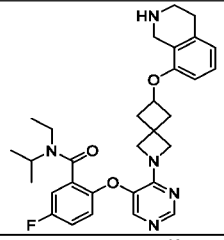
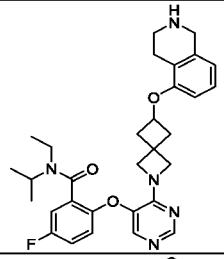
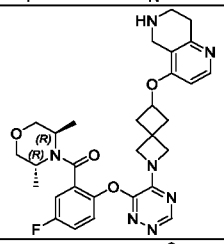
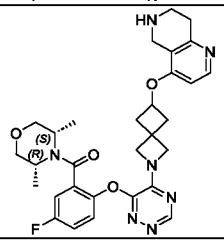
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
234		+++	+++	+++
228		+++	+++	+++
265		+++	+++	+++
281		+++	+++	+++
282		+++	+++	+++
243		+++	+++	+++
300		+++	+++	++

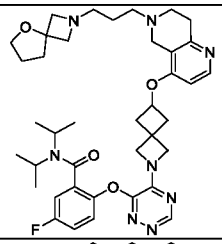
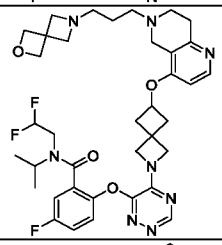
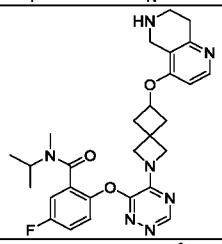
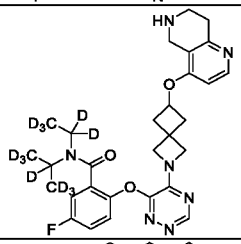
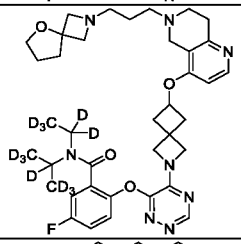
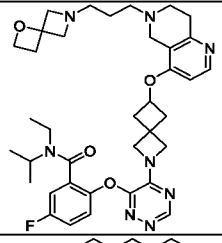
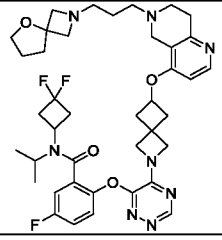
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
301		+++	+++	+++
161		+++	+++	+++
166		+++	+++	+++
186		+++	+++	+++
86-a		+++	+++	+++
118-a		+++	+++	+++
278-a		+++	+++	+++

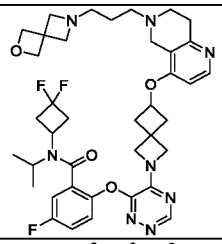
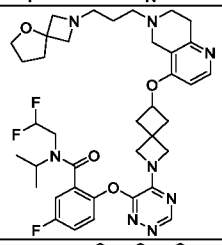
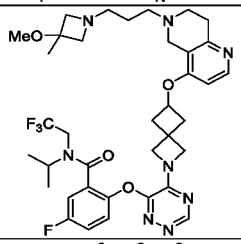
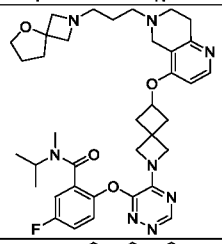
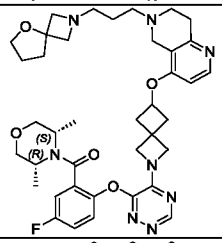
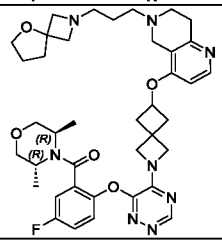
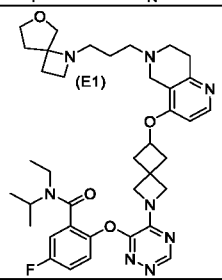
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
124		+++	+++	+++
104		+++	+++	+++
122		+++	+++	+++
114		+++	+++	+++
167		+++	+++	+++
182		+++	+++	+++

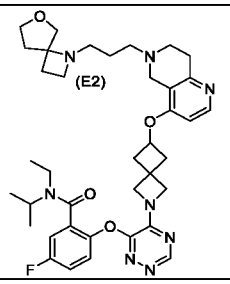
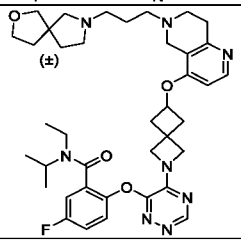
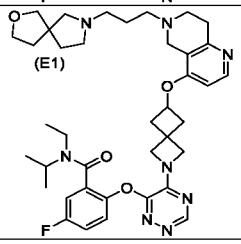
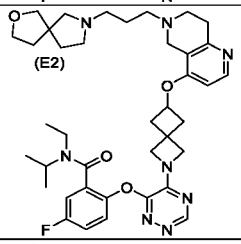
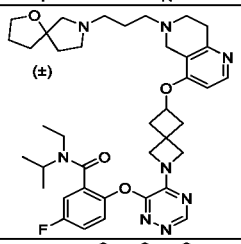
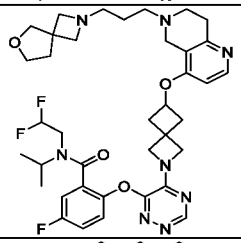
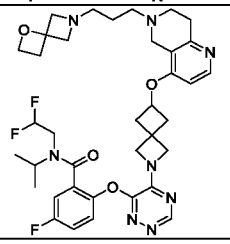
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
226		+++	+++	+++
184		+++	+++	+++
160		+++	+++	+++
78		+++	+++	+++
171		+++	+++	+++
177-a		+++	+++	+++

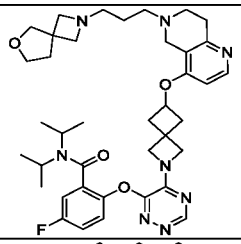
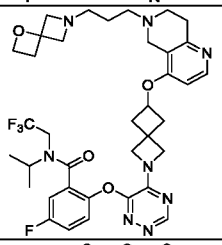
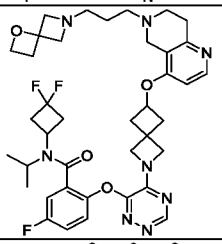
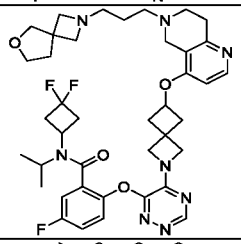
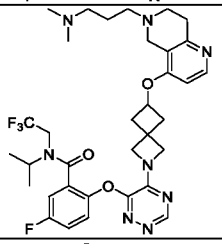
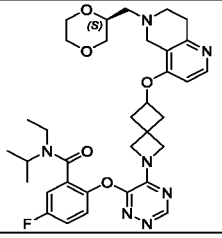
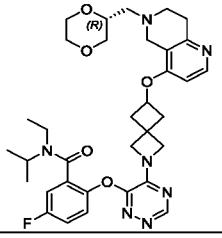
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
178-a	 (Isomer 2)	+++	+++	+++
140	 (67% E1 33% E2)	+++	+++	+++
135	 (40% E1 60% E2)	+++	+++	+++
165	 (Isomer 1)	+++	+++	+++
173	 (Isomer 2)	+++	+++	+++
306	(Isomer 1) 	+++	+++	++
307	(Isomer 2) 	+++	+++	+++

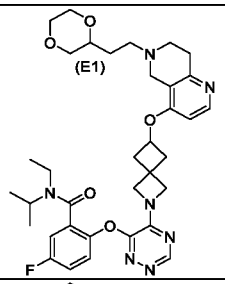
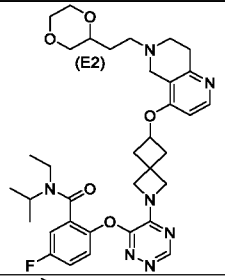
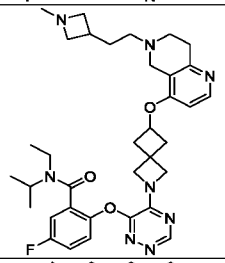
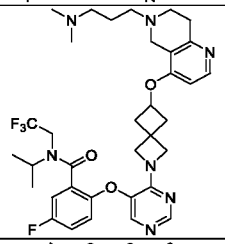
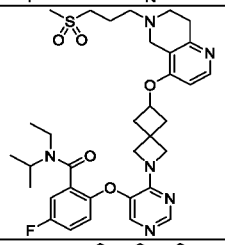
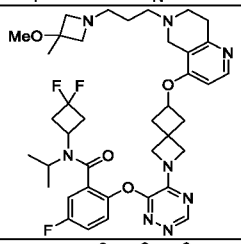
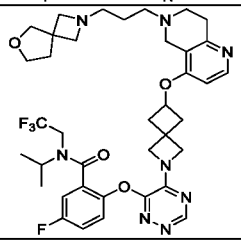
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
304		+++	+++	++
305		+++	+++	+++
342		+++	+++	+++
12		+++	+++	n/a
14		+++	+++	n/a
343		+++	+++	+++
344		+++	+++	+++

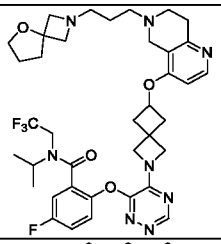
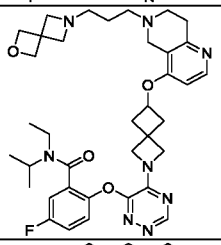
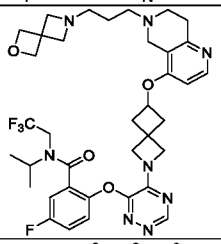
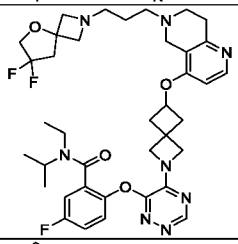
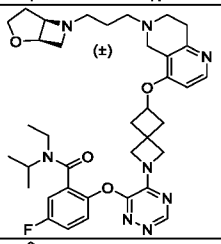
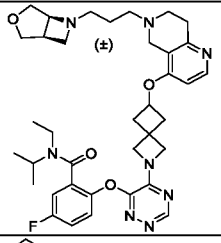
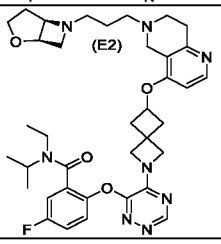
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
345		+++	+++	+++
346		+++	+++	+++
347		+++	+++	++
348		+++	+++	+++
349		+++	+++	+++
335		+++	+++	+++
350		+++	+++	+++

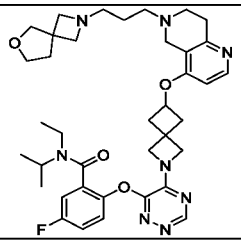
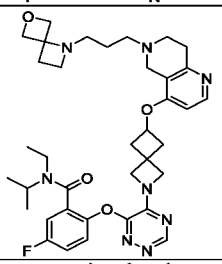
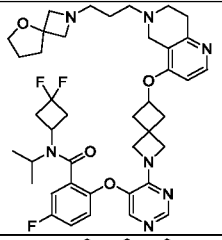
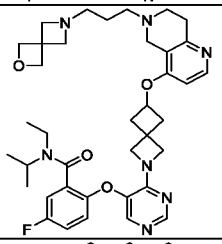
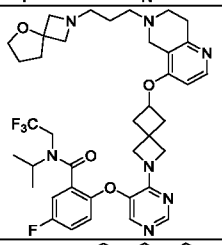
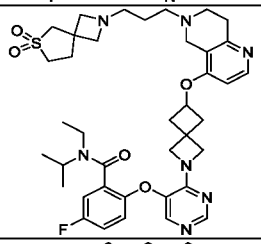
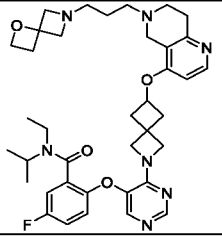
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
351		+++	+++	+++
352		+++	+++	+++
318		+++	+++	+++
353		+++	+++	++
354		+++	+++	+++
355		+++	+++	+++
356		+++	+++	+++

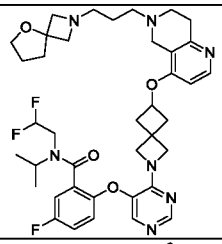
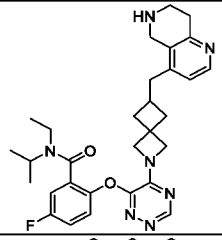
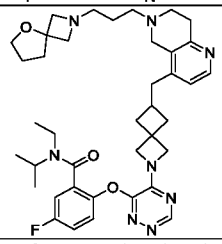
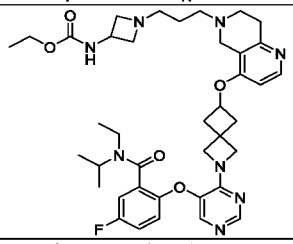
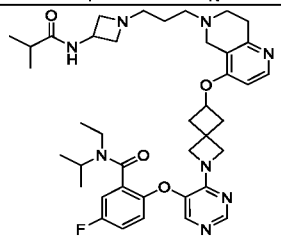
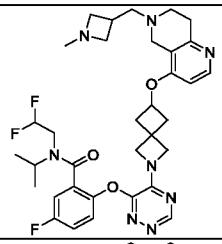
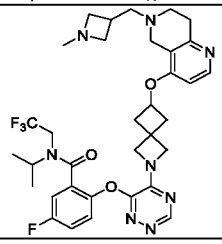
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
357		+++	+++	+++
358		+++	+++	+++
359		+++	+++	+++
360		+++	+++	+++
361		+++	+++	+++
362		+++	+++	+++
363		+++	+++	+++

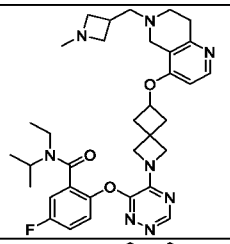
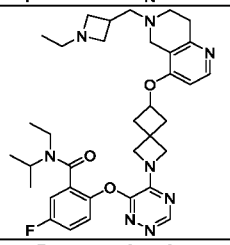
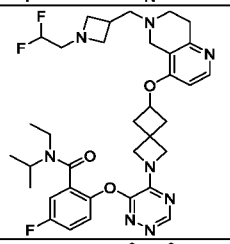
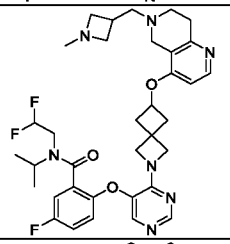
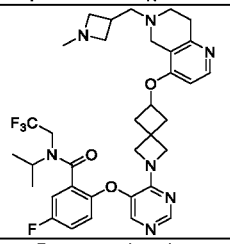
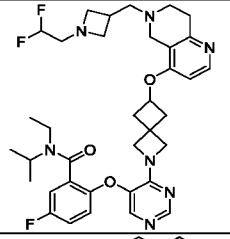
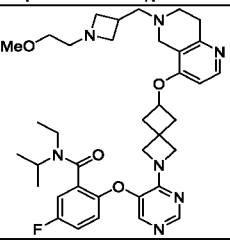
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
364		+++	+++	+++
365		+++	+++	+++
366		+++	+++	+++
367		+++	+++	+++
319		+++	+++	+++
368		+++	+++	++
369		++	+++	++

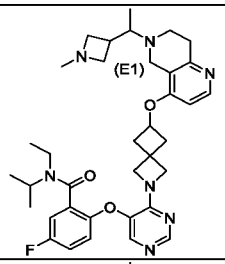
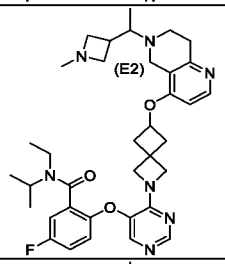
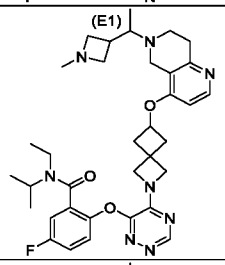
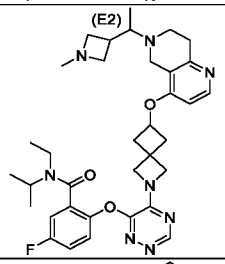
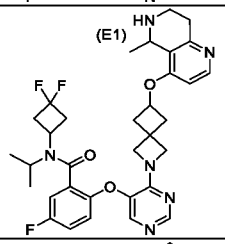
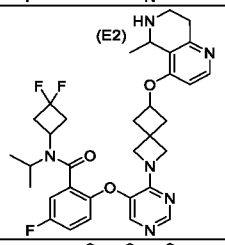
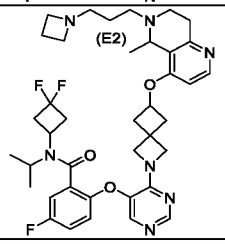
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
370		+++	+++	+++
371		+++	+++	+++
325		+++	+++	+++
372		+++	+++	+++
373		+++	+++	+++
312		+++	+++	+++
323		+++	+++	+++

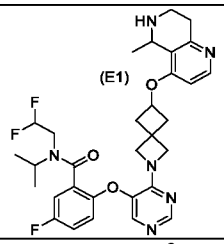
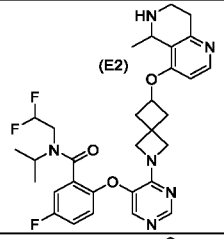
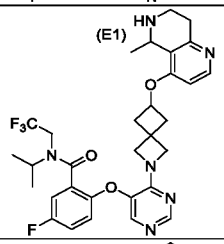
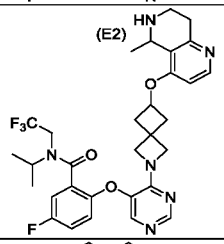
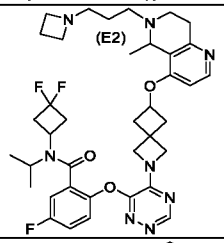
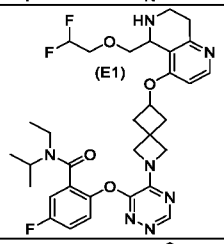
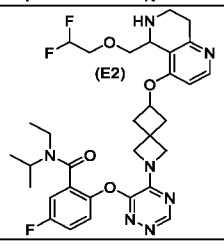
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
324		+++	+++	+++
332		+++	+++	+++
374		+++	+++	+++
375		+++	+++	+++
376		+++	+++	+++
377		+++	+++	+++
378		+++	+++	+++

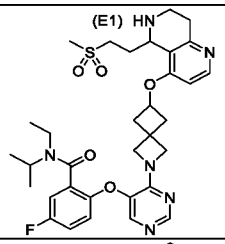
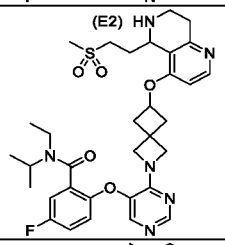
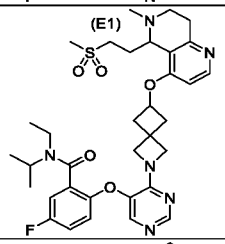
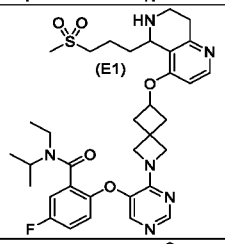
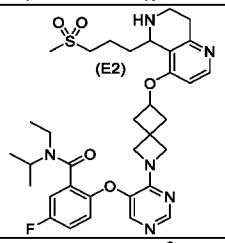
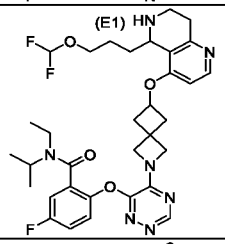
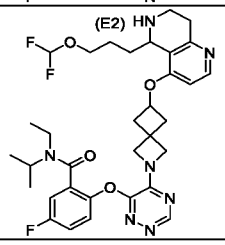
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
322		+++	+++	+++
379		+++	+++	+++
380		+++	+++	+++
381		+++	+++	+++
382		+++	+++	+++
383		+++	+++	+++
384		+++	+++	+++

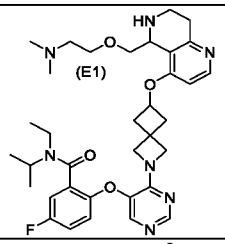
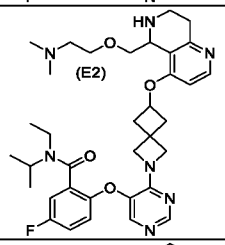
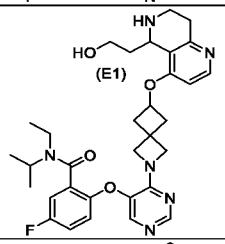
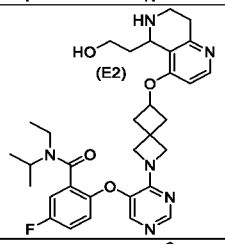
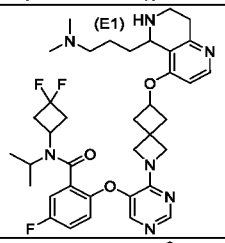
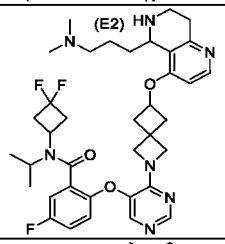
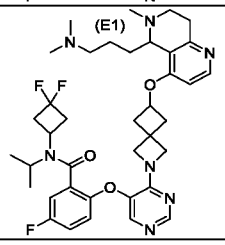
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
338		+++	+++	+++
385		+++	+++	+++
386		+++	+++	+++
197		+++	+++	+++
185		+++	+++	+++
387		+++	+++	+++
315		+++	+++	+++

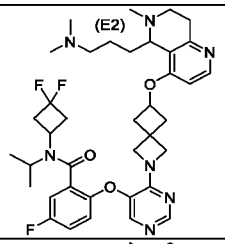
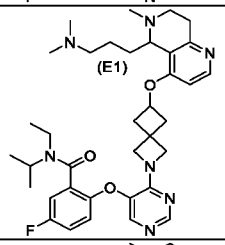
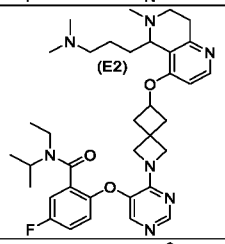
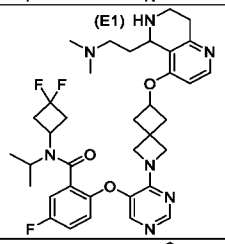
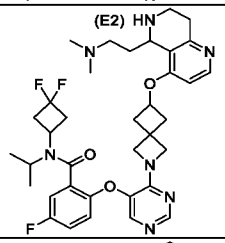
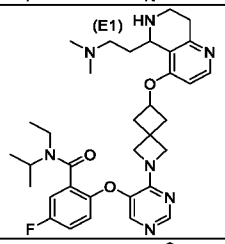
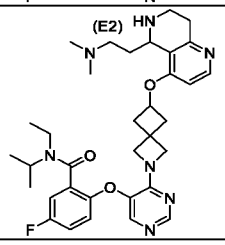
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
337		+++	+++	+++
388		+++	+++	+++
389		+++	+++	+++
341		+++	+++	+++
390		+++	+++	+++
391		+++	+++	+++
392		+++	+++	+++

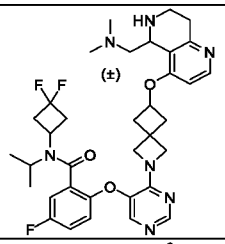
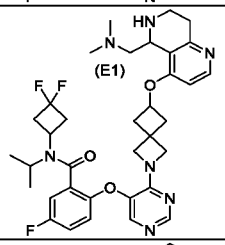
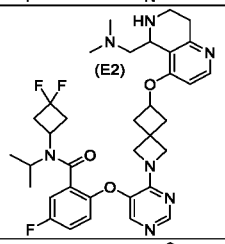
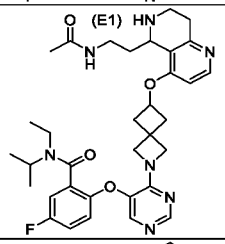
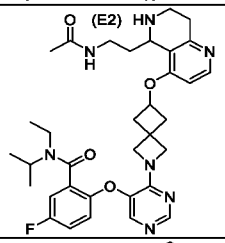
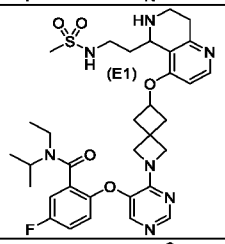
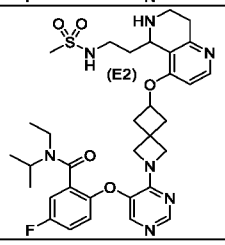
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
393		+++	+++	+++
394		+++	+++	+++
395		+++	+++	+++
396		+++	+++	+++
308		+++	+++	+++
309		+++	+++	+++
327		+++	+++	+++

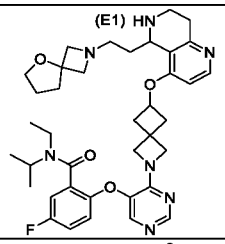
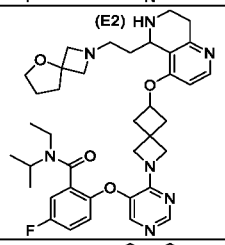
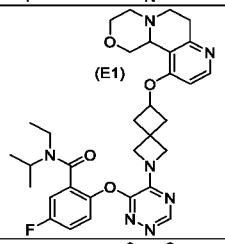
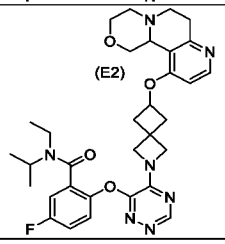
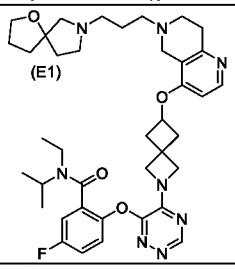
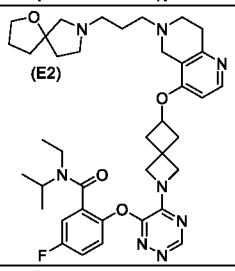
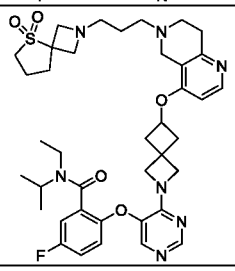
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
339		+++	+++	+++
340		+++	+++	+++
397		+++	+++	++
398		+++	+++	+++
336		+++	+++	+++
399		+++	++	++
400		+++	+++	+++

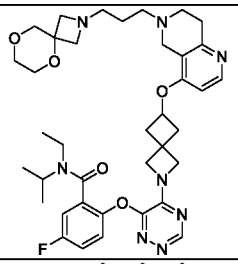
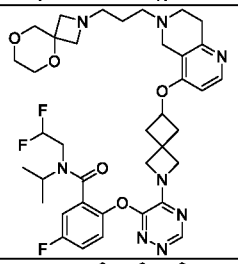
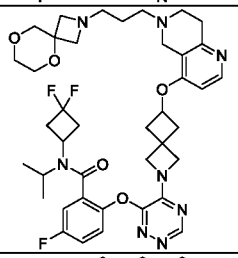
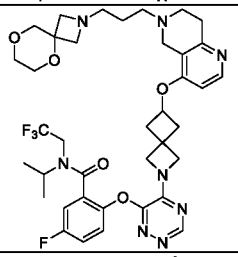
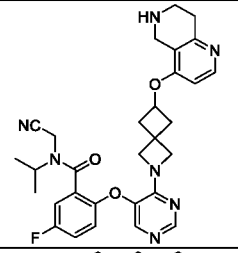
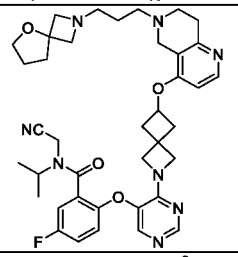
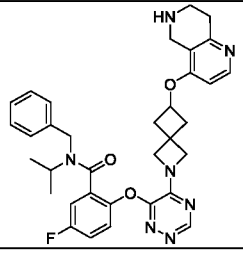
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
401		+++	+++	+++
402		++	++	++
403		+++	++	++
404		+++	+++	++
405		+++	++	++
406		+++	+++	++
407		+++	+++	+++

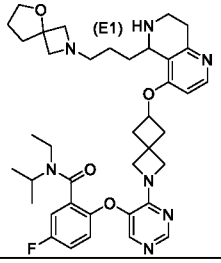
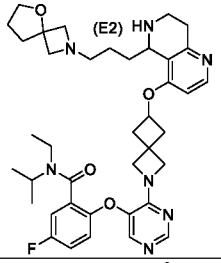
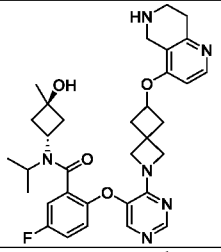
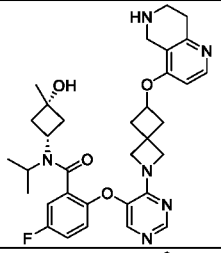
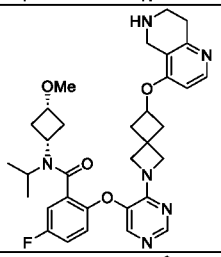
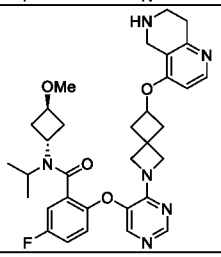
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
408		+++	+++	++
409		+++	+++	+++
410		+++	+++	++
411		+++	+++	+++
316		+++	+++	+++
317		+++	+++	+++
326		+++	+++	+++

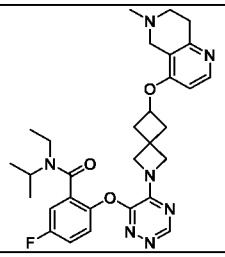
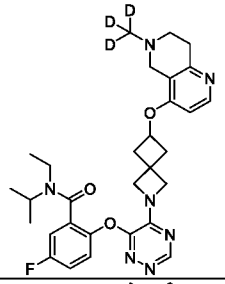
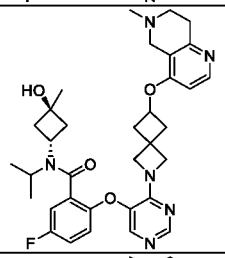
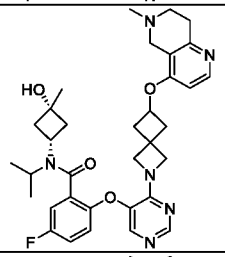
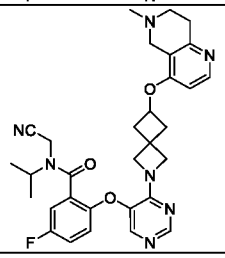
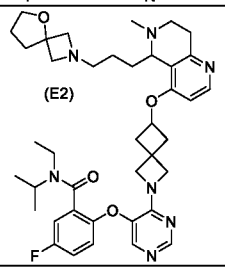
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
331		+++	+++	+++
412		+++	+++	++
413		+++	+++	+++
313		+++	+++	++
314		+++	+++	+++
328		+++	+++	++
329		+++	+++	+++

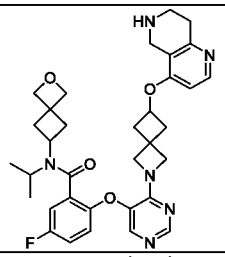
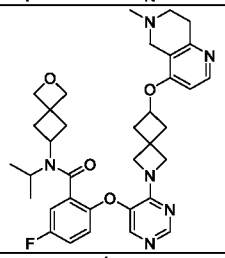
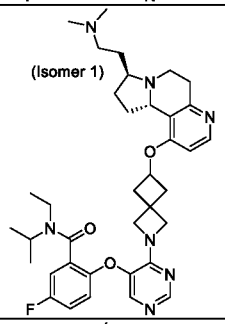
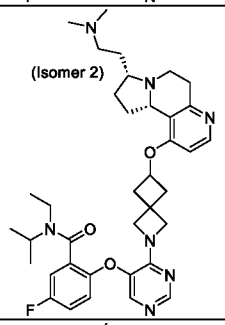
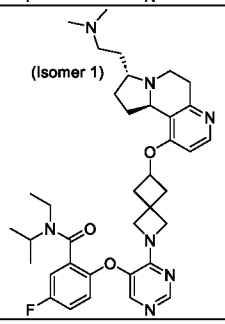
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
330		+++	+++	+++
333		++	+++	++
334		+++	+++	+++
414		+++	+++	++
415		+++	++	++
416		+++	+++	++
417		+++	++	++

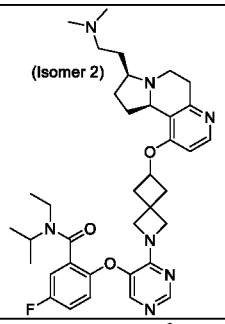
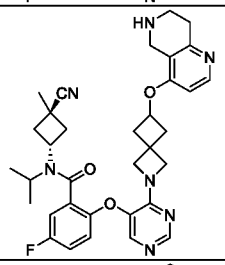
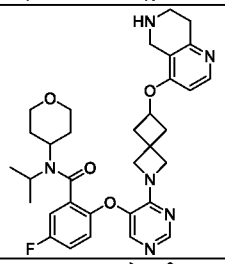
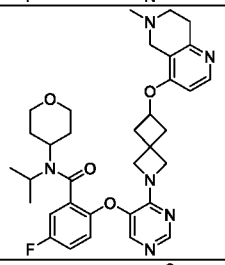
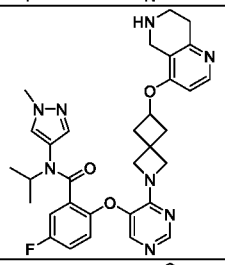
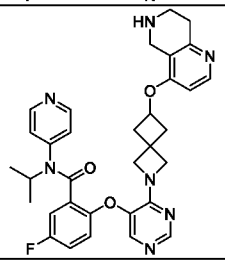
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
418		+++	++	++
419		+++	+++	+++
420		+	++	+
421		+++	+++	++
422		+++	+++	+++
423		+++	+++	+++
424		+++	+++	+++

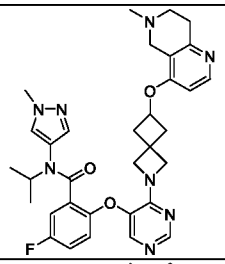
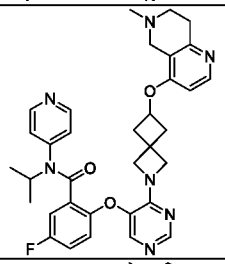
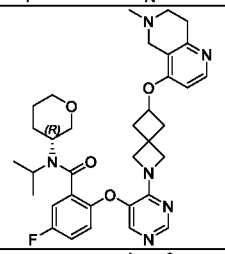
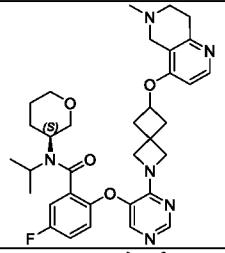
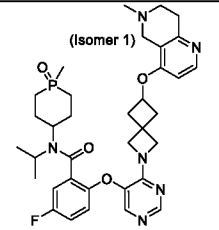
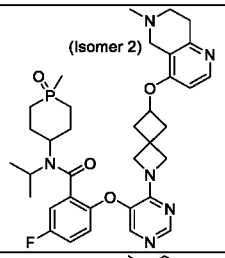
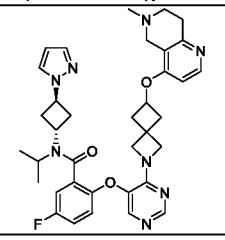
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
425		+++	+++	+++
426		+++	+++	+++
427		+++	+++	+++
428		+++	+++	+++
429		+++	+++	+++
430		+++	+++	+++
431		+	+++	++

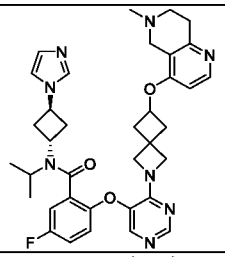
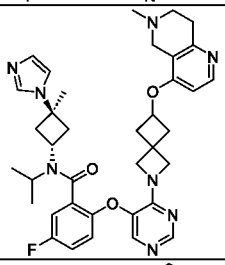
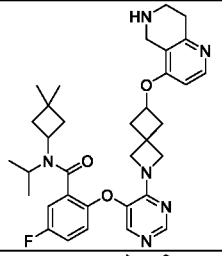
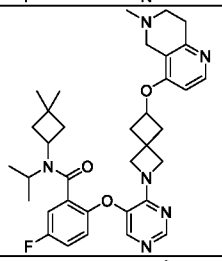
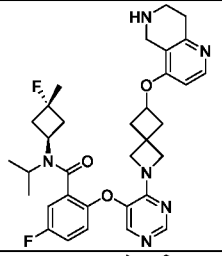
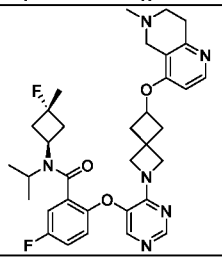
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
432		+++	+++	++
433		+++	+++	+++
434		+++	+++	+++
435		+++	+++	+++
436		+++	+++	+++
437		+++	+++	+++

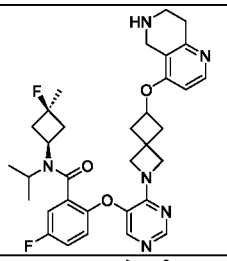
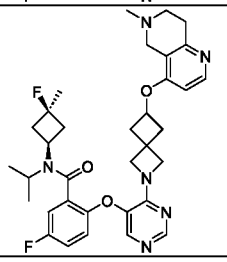
Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
438		+++	+++	+++
439		+++	+++	+++
440		+++	+++	+++
441		+++	+++	+++
442		+++	+++	+++
443		+++	+++	+++

Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
444		+++	+++	+++
445		+++	+++	+++
446		+++	+++	++
447		+++	+++	+++
448		+++	+++	+++

Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
449		+++	+++	+++
450		+++	+++	+++
451		+++	+++	+++
452		+++	+++	+++
453		+++	++	+++
454		+++	+++	++

Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
455		+++	+++	+++
456		+++	+++	+++
457		+++	+++	+++
458		+++	+++	+++
459		+++	+	+
460		+++	+	+
461		+++	+++	+++

Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
462		+++	+++	+++
463		+++	+++	+++
464		+++	+++	+++
465		+++	+++	+++
466		+++	+++	+++
467		+++	+++	+++

Compound No.	Structure	WT Menin Ki (nM)	MV4;11 EC_{50} (nM)	MV4;11 M327I (het) EC_{50} (nM)
468		+++	+++	+++
469		+++	+++	+++

Example 473. Patch Clamp Assay

The 35 mm culture dishes upon which cells were seeded at a density allowing single cells to be recorded were placed on the dish holder of the microscope and continuously perfused (at approximately 1 mL/min) with the bath solution. All solutions applied to cells including the pipette solution were maintained at room temperature (19°C to 30°C). After formation of a Gigaohm seal between the patch electrodes and individual hERG stably transfected HEK 293 cells (pipette resistance range: 2.0 MΩ to 7.0 MΩ; seal resistance range: > 1GΩ) the cell membrane across the pipette tip was ruptured to assure electrical access to the cell interior (whole-cell patch-configuration). In case the quality of the seal was poor, the process of seal formation was repeated with a different cell and a new pipette. As soon as a stable seal could be established, hERG outward tail currents were measured upon depolarization of the cell membrane to +20 mV for 2s (activation of channels) from a holding potential of -80 mV and upon subsequent repolarization to -40 mV for 3 s. This voltage protocol (as shown below) was run at least 10 times at intervals of 10 s. If current density was judged to be too low for measurement, another cell was recorded.

Once control recordings have been accomplished, cells were continuously perfused with a bath solution containing the test item 0.3% DMSO or 100 nM E-4031. During wash-in of the test item the voltage protocol indicated above was run continuously again at 10 s intervals until the steady-state level of block was reached.

EQUIVALENTS

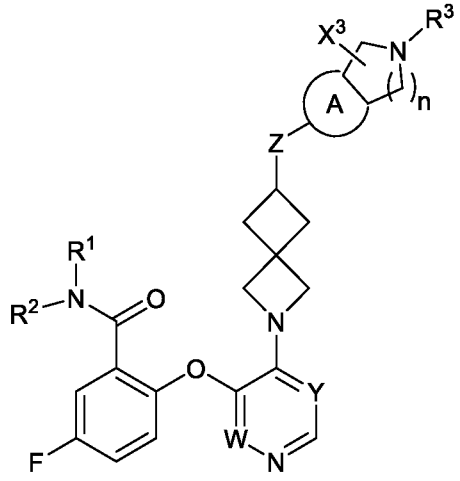
While we have described a number of embodiments of this disclosure, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this disclosure. The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art. The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto. The references cited herein are not admitted to be prior art to the application.

The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred 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 include plural referents 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 by reference.

CLAIMS

What is claimed is:

1. A compound of Formula (I),



Formula (I),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$;

R^1 and R^2 optionally form a 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, or CN;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

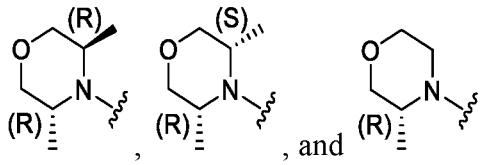
n is 1, 2, or 3.

2. The compound of claim 1, wherein R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$.

3. The compound of claim 1 or 2, wherein R^2 is C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, OH, oxo, CN, or $N(R^{4a'})(R^{4b'})$.

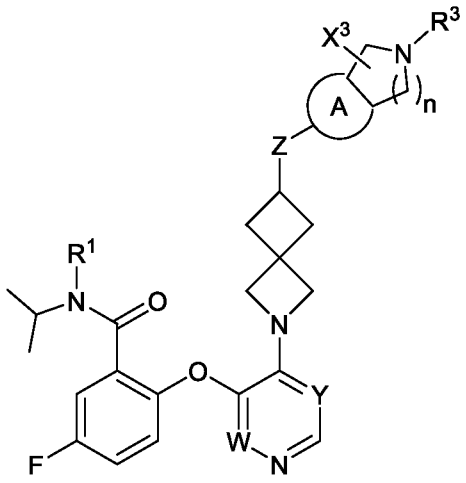
4. The compound of any one of the preceding claims, wherein R^2 is isopropyl.

5. The compound of claim 1, wherein R^1 and R^2 form a group selected from:



, , and .

6. A compound of Formula (II),



Formula (II),

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

W is N or CH;

Y is N or CH;

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy;

X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$;

R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, or

R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a};

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$;

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl; and

n is 1, 2, or 3.

7. The compound of any one of the preceding claims, wherein W is N.

8. The compound of any one of the preceding claims, wherein W is CH.

9. The compound of any one of the preceding claims, wherein Y is N.

10. The compound of any one of the preceding claims, wherein Y is CH.

11. The compound of any one of the preceding claims, wherein R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$.

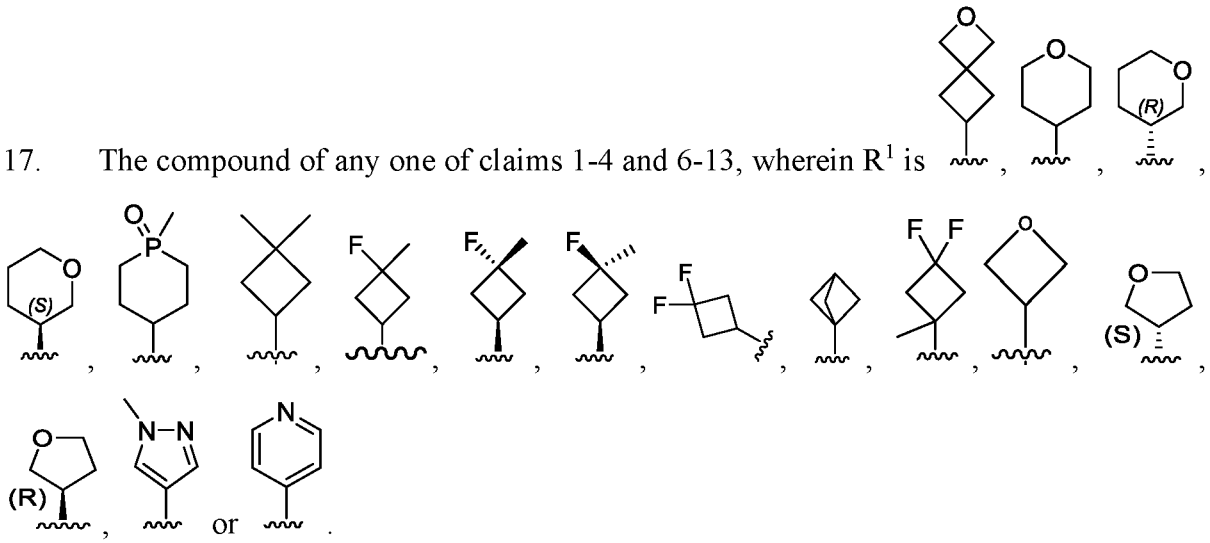
12. The compound of any one of the preceding claims, wherein R^1 is C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, the C_3-C_{12} cycloalkyl, or the 3- to 12-membered heterocyclyl is optionally substituted with one or more halo, OH, oxo, CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $N(R^{4a'})(R^{4b'})$.

13. The compound of any one of the preceding claims, wherein R^1 is C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, the C_3-C_{12} cycloalkyl, or the 3- to 12-membered heterocyclyl is optionally substituted with one or more halo.

14. The compound of any one of claims 1-4 and 6-13, wherein R^1 is methyl or ethyl.

15. The compound of any one of claims 1-4 and 6-13, wherein R^1 is isopropyl.

16. The compound of any one of claims 1-4 and 6-13, wherein R^1 is 2,2-difluoroethyl.

17. The compound of any one of claims 1-4 and 6-13, wherein R^1 is .

18. The compound of any one of claims 1-4 and 6-13, wherein R^1 is -CH_2-CN, or -CH_2-phenyl.

19. The compound of any one of claims 1-4 and 6-12, wherein R^1 is cyclobutyl substituted by one OH and one methyl group, cyclobutyl substituted by one CN and one methyl group, cyclobutyl substituted by one methoxy group, cyclobutyl substituted by one 1H-pyrazol-1-yl group, cyclobutyl substituted by one 1H-imidazol-1-yl group, or cyclobutyl substituted by one 1H-imidazol-1-yl group and one methyl group.

20. The compound of any one of the preceding claims, wherein Z is O, CH_2, or NH.

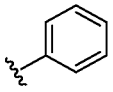
21. The compound of any one of the preceding claims, wherein Z is O.

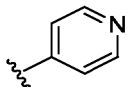
22. The compound of any one of claims 1-20, wherein Z is CH_2.

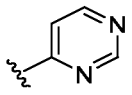
23. The compound of any one of claims 1-20, wherein Z is NH.

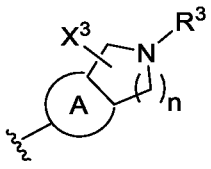
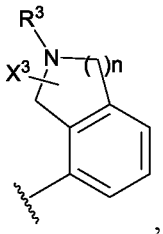
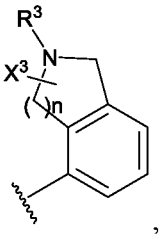
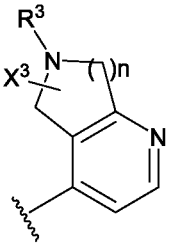
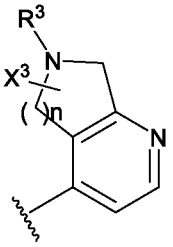
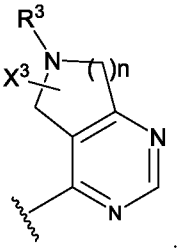
24. The compound of any one of the preceding claims, wherein Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl, wherein the 6- to 10-membered aryl or 6- to 10-membered heteroaryl is optionally substituted with one or more C_1-C_6 alkyl, halo, OH, CN, or C_1-C_6 alkoxy.

25. The compound of any one of the preceding claims, wherein Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl.

26. The compound of any one of the preceding claims, wherein Ring A is .

27. The compound of any one of claims 1-25, wherein Ring A is .

28. The compound of any one of claims 1-25, wherein Ring A is .

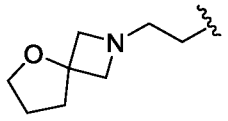
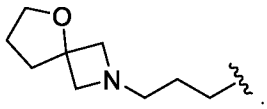
29. The compound of any one of the preceding claims, wherein  is , , , , or .

30. The compound of any one of the preceding claims, wherein X^3 is H, C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more halo, 3- to 12-membered heterocyclyl, $S(=O)_2R^{4a}$, OR^{4a}, oxo, CN, $C(=O)N(R^{4a})(R^{4b})$, or $N(R^{4a})(R^{4b})$,and wherein

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2$-$N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$.

31. The compound of any one of the preceding claims, wherein X^3 is H or C_1-C_6 alkyl.

32. The compound of claims 1-30, wherein X^3 is $-CH_2-OCH_3$, $-CH_2-CH_2-OCH_3$, $-CH_2-CH_2-CH_2-OCH_3$, $-CH_2-O-CH_2-CHF_2$, $-CH_2-CH_2-CH_2-O-CHF_2$, $-CH_2-O-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-S(O)_2-CH_3$ or $-CH_2-CH_2-CH_2-S(O)_2-CH_3$, $-CH_2-CH_2-NH-C(O)-CH_3$, $-CH_2-CH_2-NH-S(O)_2-CH_3$, or  , or  .

33. The compound of claims 1-31, wherein X^3 is methyl.

34. The compound of any one of the preceding claims, wherein R^3 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl is optionally substituted with one or more R^{3a}, wherein:

each R^{3a} is independently halo, OR^{4a}, oxo, $C(O)O(R^{4a})$, CN, $C(=O)N(R^{4a})(R^{4b})$, $OC(O)N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, $N(R^{4a})(R^{4b})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl is optionally substituted with one or more substituent independently selected from halo, $O(R^{4a'})$, oxo, CN, $C(O)OR^{4a'}$, $OC(O)N(R^{4a'})(R^{4b'})$, $N(R^{4a'})(R^{4b'})$, $N(R^{4a'})C(O)(R^{4b'})$, $N(R^{4a'})C(O)O(R^{4b'})$, C_1-C_6 alkyl that is optionally substituted with $O(R^{4a})$, and 3- to 12-membered heterocyclyl that is optionally substituted with oxo;

each R^{4a} is independently H, CN, or C_1-C_6 alkyl optionally substituted with one or more halo, C_6-C_{10} aryl or $N(R^{4a'})(R^{4b'})$;

each R^{4b} is independently H, $S(=O)_2R^{4b'}$, $C(O)OR^{4b'}$, $C(O)R^{4b'}$, $C(O)NR^{4a'}R^{4b'}$, $C(O)CH_2-N(R^{4a'})(R^{4b'})$, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $C_{6\text{-}10}$ aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl is optionally substituted with C_1-C_6 alkoxy or $C(O)N(R^{4a'})(R^{4b'})$; and

each $R^{4a'}$ and $R^{4b'}$ is independently H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocyclyl.

35. The compound of any one of claims 1-34, wherein R^3 is C_1-C_6 alkyl that is optionally substituted with one or more R^{3a}, wherein:

each R^{3a} is independently $N(R^{4a})(R^{4b})$, $S(=O)_2R^{4b'}$, or 3- to 12-membered heterocyclyl that is optionally substituted with one or more substituent independently selected from C_1-C_6 alkyl optionally substituted with one or more halo, and $O(R^{4a'})$;

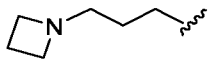
each R^{4a} and R^{4b} is independently H, or C_1-C_6 alkyl; and

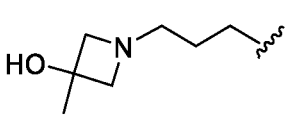
each $R^{4a'}$ and $R^{4b'}$ is independently H or C_1-C_6 alkyl.

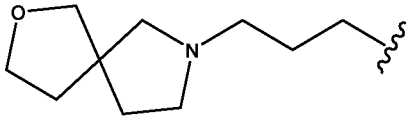
36. The compound of any one of claims 1-35, wherein R^3 is methyl, ethyl, or isopropyl.

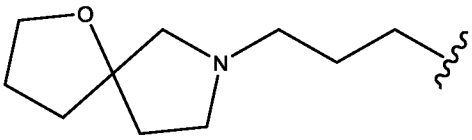
37. The compound of any one of claims 1-34, wherein R^3 is $-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$, $-CH_2-CH_2-S(=O)_2Me$, or $-CH_2-CH_2-CH_2-S(=O)_2Me$.

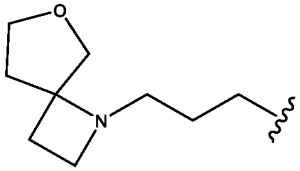
38. The compound of any one of claims 1-34, wherein R^3 is H.

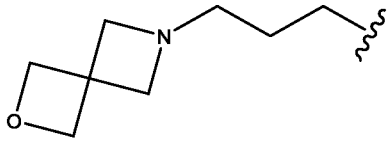
39. The compound of any one of claims 1-34, wherein R^3 is ,

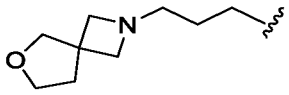
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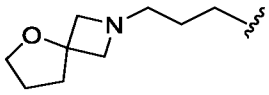
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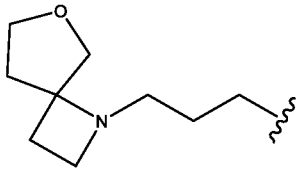
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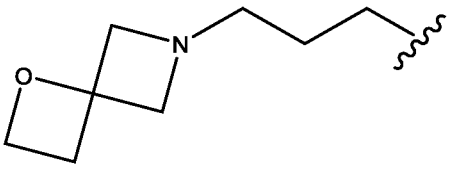
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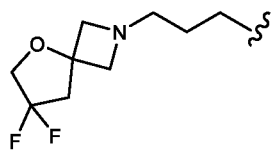
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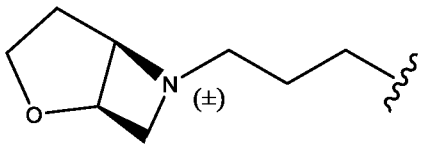
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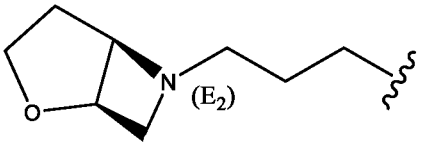
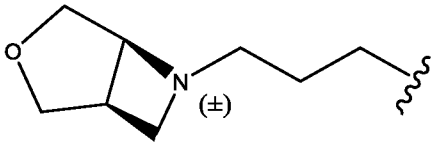
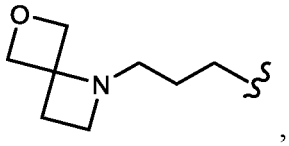
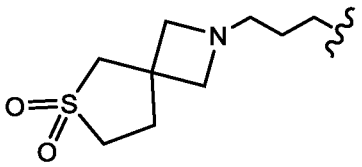
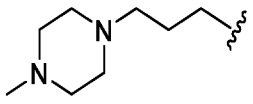
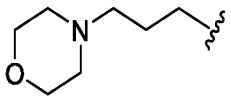
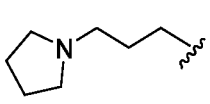
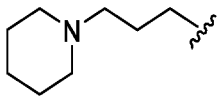
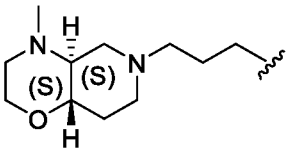
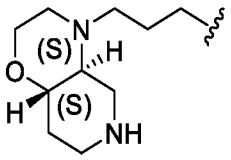
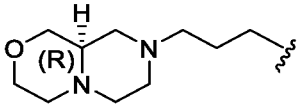
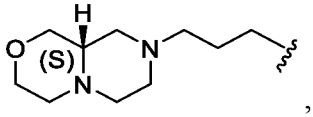
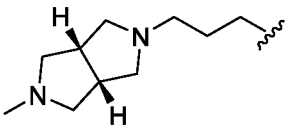
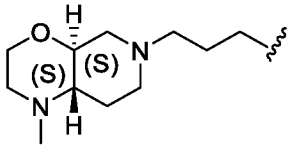
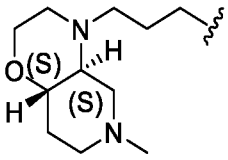
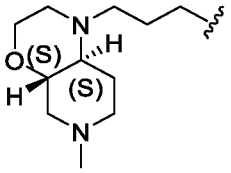
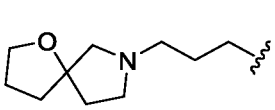
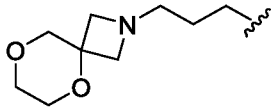
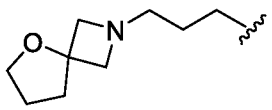
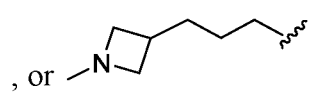
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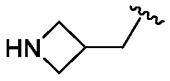
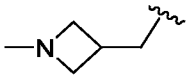
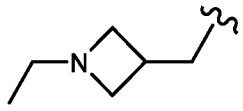
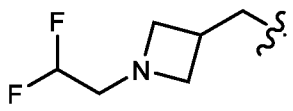
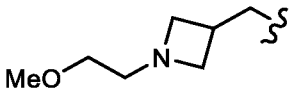
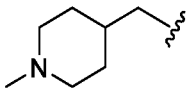
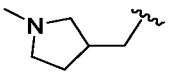
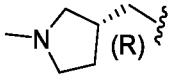
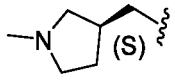
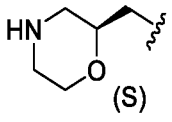
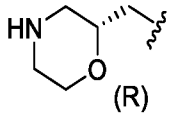
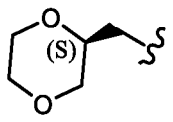
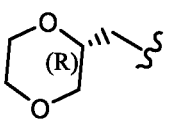
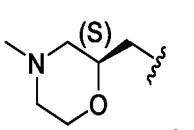
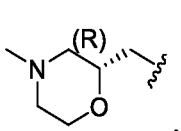
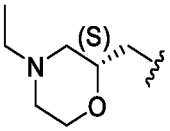
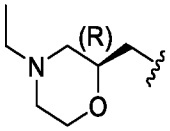
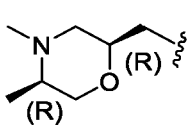
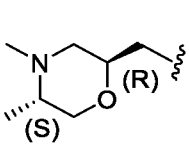
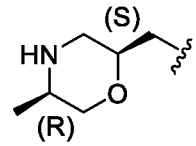
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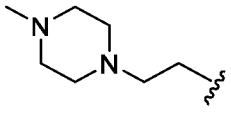
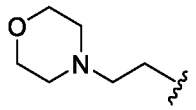
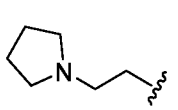
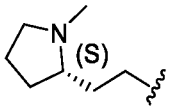
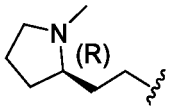
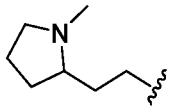
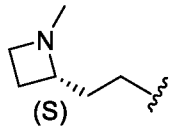
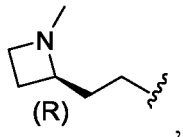
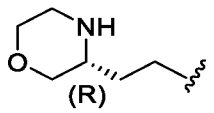
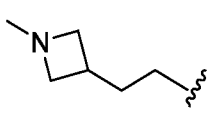
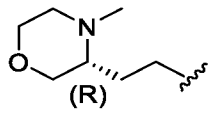
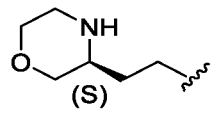
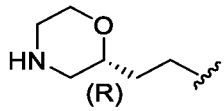
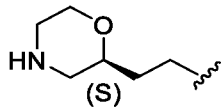
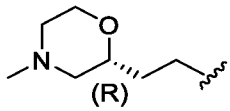
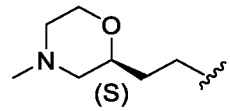
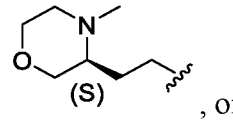
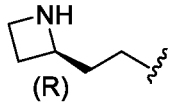
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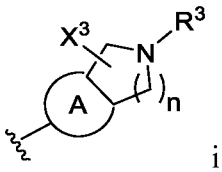
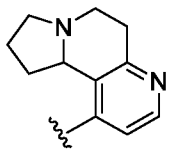
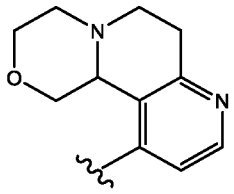





















40. The compound of any one of claims 1-34, wherein R^3 is , , , , , , , , , , , , , , , , , , , , , , or .

41. The compound of any one of claims 1-34, wherein R^3 is , , , , , , , , , , , , , , , , , or .

42. The compound of any one of claims 1-34, wherein R^3 is H.

43. The compound of any one of claims 1-33, wherein R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected.

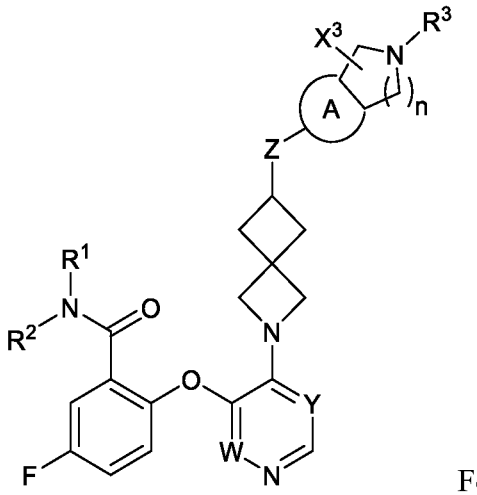
44. The compound of claim 43, wherein  is , or .

45. The compound of any one of the preceding claims, wherein n is 1.

46. The compound of any one of the preceding claims, wherein n is 2.

47. The compound of any one of the preceding claims, wherein n is 3.

48. A compound of Formula (III),



Formula (III),

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

W is N or CH;

Y is N or CH;

R^1 is C_1-C_6 alkyl or C_3-C_{12} cycloalkyl, wherein the C_1-C_6 alkyl or the C_3-C_{12} cycloalkyl is optionally substituted with one or more halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl;

Z is O, CH_2, or NH;

Ring A is 6- to 10-membered aryl or 6- to 10-membered heteroaryl;

X^3 is H or C_1-C_6 alkyl;

R^3 is H or C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more R^{3a} or R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected;

each R^{3a} is independently $N(R^{4a})(R^{4b})$ or 3- to 12-membered heterocyclyl, wherein the 3- to 12-membered heterocyclyl is optionally substituted with one or more substituent independently selected from C_1-C_6 alkyl and $O(R^{4a'})$;

each R^{4a} and R^{4b} is independently C_1-C_6 alkyl;

$R^{4a'}$ is H; and

n is 1 or 2.

49. The compound of claim 48, wherein W is N.

50. The compound of claim 48, wherein W is CH.

51. The compound of any one of claims 48-50, wherein Y is N.

52. The compound of any one of claims 48-50, wherein Y is CH.

53. The compound of any one of claims 48-52, wherein R^1 is C_1-C_6 alkyl optionally substituted with one or more halo.

54. The compound of any one of claims 48-52, wherein R^1 is C_3-C_{12} cycloalkyl optionally substituted with one or more halo.

55. The compound of any one of claims 48-54, wherein R^2 is C_1-C_6 alkyl.

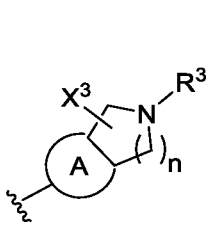
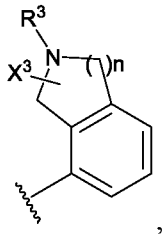
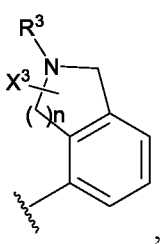
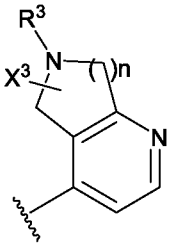
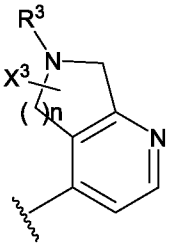
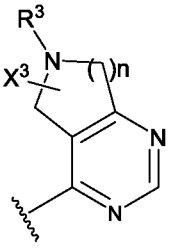
56. The compound of any one of claims 48-54, wherein R^2 is C_1-C_6 alkyl.

57. The compound of any one of claims 48-56, wherein Z is O.

58. The compound of any one of claims 48-56, wherein Z is NH.

59. The compound of any one of claims 48-56, wherein Z is CH_2.

60. The compound of any one of claims 48-59, wherein Ring A is 6-membered aryl or 6-membered heteroaryl.

61. The compound of any one of claims 48-59, wherein  is , , , , or .

62. The compound of any one of claims 48-61, wherein X^3 is H.

63. The compound of any one of claims 48-61, wherein X^3 is C_1-C_6 alkyl.

64. The compound of any one of claims 48-63, wherein R^3 is H.

65. The compound of any one of claims 48-63, wherein R^3 is C_1-C_6 alkyl optionally substituted with one or more R^{3a}.

66. The compound of claim 65, wherein R^{3a} is $N(R^{4a})(R^{4b})$ and wherein each R^{4a} and R^{4b} is independently C_1-C_6 alkyl.

67. The compound of claim 65, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl optionally substituted with one or more substituent independently selected from C_1-C_6 alkyl and $O(R^{4a'})$.

68. The compound of claim 67, wherein each R^{3a} is independently 3- to 12-membered heterocyclyl optionally substituted with one or more substituent independently selected from C_1-C_6 alkyl and OH.

69. The compound of any one of claims 48-63, wherein R^3 forms a 3- to 12-membered heterocyclyl with the carbon atom next to the nitrogen atom to which it is connected.

70. The compound of any one of claims 48-69 wherein n is 1.

71. The compound of any one of claims 48-69 wherein n is 2.

72. A compound as shown in Table 1 or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

73. A compound as shown in Table 1 or a pharmaceutically acceptable salt thereof.

74. A compound as shown in Table 1.

75. A compound as shown in Table 1 or a pharmaceutically acceptable salt thereof, wherein the salt is hydrochloric acid.

76. The compound according to any one of the preceding claims, wherein the compound is useful for the treatment of a cancer and wherein the compound minimizes hERG binding.

77. A pharmaceutical composition comprising a compound of any one of claims 1 to 49, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

78. A pharmaceutical composition comprising a salt or crystalline form of any one of claims 1-48, and at least one pharmaceutically acceptable carrier.

79. A method of inhibiting the interaction between menin and MLL comprising contacting the menin and MLL with a compound of any one of claims 1 to 76 or a pharmaceutical composition of either claim 77 or 78.

80. A method of treating cancer in a patient comprising administering to the patient a compound of any one of claims 1 to 76 or a pharmaceutical composition of either claim 77 or 78.

81. The method of claim 80, wherein the cancer is a hematological cancer.

82. The method of either claim 80 or 81, wherein the cancer is a leukemia.

83. The method of either claim 80 or 81, wherein the cancer is a lymphoma.

84. The method of either claim 80 or 81, wherein the cancer is mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage (KMT2A-rearranged) leukemia (MLL-r), leukemia associated with a MLL rearrangement or a rearrangement of the *MLL* gene, acute leukemia, chronic leukemia, indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute granulocytic leukemia, acute

nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), therapy related leukemia, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), myeloproliferative neoplasia (MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sézary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma, Hodgkin's lymphoma, non Hodgkin's lymphoma (malignant lymphoma), or Waldenstrom's macroglobulinemia.

85. The method of either claim 80 or 81, wherein the cancer is an abstract nucleophosmin (NPM1)-mutated acute myeloid leukemia (*i.e.*, $NPM1^{mut}$ acute myloid leukemia).

86. The method of either claim 80 or 81, wherein the cancer is a rearranged mixed lineage (KMT2A-rearranged) leukemia (MLL-r).

87. A compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78, for use in treating or preventing a disease caused by, or associated with, menin expression, activity, and/or function.

88. A compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78, for use in treating or preventing cancer.

89. Use of a compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78, for treating or preventing a disease caused by, or associated with, menin expression, activity, and/or function.

90. Use of a compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78, in the manufacture of a medicament for treating or preventing a disease caused by, or associated with, menin expression, activity, and/or function.

91. Use of a compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78, for treating or preventing cancer.

92. Use of a compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78, in the manufacture of a medicament for treating or preventing cancer.

93. A kit comprising a compound of any of claims 1-76 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of either claim 77 or 78 and instructions for its use.